PATENT

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APPLICATION FOR UNITED STATES LETTERS PATENT

for

TREATMENT OF PATIENTS WITH MULTIPLE SCLEROSIS BASED ON GENE EXPRESSION CHANGES IN CENTRAL NERVOUS SYSTEM TISSUES

by

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BACKGROUND OF THE INVENTION

The present application claims benefit of priority U.S. Provisional Serial No. 60/414,219, filed September 27, 2002, the entire contents of which are hereby incorporated by reference.

1. Field of the Invention

The present invention relates generally to the fields of molecular biology, genomics, immunology and neurobiology. More particularly, it concerns the identification of specific genes that are dysregulated in patients afflicted with multiple sclerosis (MS), and the use of these genes as targets for MS therapies.

2. Description of Related Art

Multiple sclerosis (MS) continues to be a serious health problem that afflicts hundreds of thousands each year in the US alone, and millions worldwide. One of the difficult aspects of dealing with MS is identifying patients early in the course of the disease. This is difficult not only because of the lack of a definitive biological test for MS, but because the symptoms may overlap with those of numerous other diseases.

The concordance rate of multiple sclerosis among monozygotic twins is 20-40%, while the risk of a non-twin sibling of an MS patient of developing MS is 2-4%. These facts highly suggest the presence of polygenic susceptibility (nonmendelian inheritance). Although no single gene is associated with all types of MS, several reports have revealed that some genes are associated with MS in certain populations. The well known HLA association with MS has been demonstrated in populations of northern European ancestry. In the Finnish population an association with the myelin basic protein gene has been reported (Tienari *et al.*, 1992). In an European MS patient population, an association with a T cell differentiation-related antigen, CD45, has been demonstrated (Jacobsen *et al.*, 2000).

Since the disease is polymorphic (*i.e.*, not inherited in a classical mendelian pattern but clearly multiple genes are involved in leading to predisposition), recent genomic approaches have been implemented to elucidate multiple genes simultaneously that may be associated with the disease. A recent publication by Lock *et al.* (2002) demonstrates how gene expression profiling using DNA microarrays to examine MS brain tissues can help identify multiple single

genes that are associated with the disease, and may therefore serve as targets of treatment. By altering the function of the product of some of these genes in the animal model of MS, experimental autoimmune encephalomyelitis (EAE), these authors confirmed that some genes found to be altered by DNA microarray screening indeed had an impact on the severity of the disease.

Another approach to identify potential single gene associations is to examine polymorphic gene variants or single nucleotide polymorphisms (SNPs) of candidate genes, or screen the entire genome to establish the SNPs that are associated with the disease. Multiple polymorphisms have been associated with MS, as follows: (a) polymorphisms associated with MS disease susceptibility found in the following genes: SCA2 (Chataway *et al.*, 1999), interferon α (Miterski *et al.*, 1999), estrogen receptor (Niino *et al.*, 2000), plasminogen activator inhibitor 1 (Luomala *et al.*, 2000), tumor necrosis factor α (Fernandez-Arquero *et al.*, 1999; Lucotte *et al.*, 2000), monocyte chemotactic protein 3 (Fiten *et al.*, 1999), vitamin D receptor (Fukazawa *et al.*, 1999), CTLA4 (Fukazawa *et al.*, 1999), γ aminobutyric acid (Gade-Andavolu *et al.*, 1998); (b) polymorphisms associated with disease severity found in the following genes: interleukin 6 (Vandenbroeck *et al.*, 2000), IgG Fc receptor (FcγR) (Myhr *et al.*, 1999), glutathione-S-transferase (Mann *et al.*, 2000); (c) polymorphisms associated with age of onset of MS found in the following genes: interleukin 4 (Vandenbroeck *et al.*, 1997) and chemokine receptor CCR5 (Barcellos *et al.*, 2000); and (d) polymorphism associated with remyelination capacity: apolipoprotein E (Carlin *et al.*, 2000). Other gene polymorphisms that have been associated with MS include intercellular adhesion molecule 1 (ICAM-1) (Mycko *et al.*, 1998), the pro-inflammatory gene lymphotoxin (Mycko *et al.*, 1998) and immunoglobulin heavy chain gene polymorphisms (Hashimoto *et al.*, 1993; Walter *et al.*, 1991).

Despite these individual associations, there has yet to be put forth a cohesive set of genes that provide clearly relevant targets for genetic based therapies.

SUMMARY OF THE INVENTION

Thus, in accordance with the present invention, there is provided a method for treating or preventing multiple sclerosis (MS) comprising administering to a subject with MS a composition that causes an increase in the level of a gene product selected from the group consisting of those genes indicated by a minus (-) sign in Tables 1-15, except those indicated by asterisk(s). In still yet a further embodiment, there is provided a method for treating or preventing multiple sclerosis (MS) comprising administering to a subject with MS a composition that causes a decrease in the level of a gene product selected from the group consisting of those genes indicated by a plus (+) sign in Tables 1-15, except those indicated by asterisk(s). Further, genes from Table 16, 17, or 18 are lists of genes previously reported to be associated with MS central nervous system tissues by Lock *et al.* (2002), Chabas *et al.* (2001), and Whitney *et al.* (1999), respectively, and are indicated by asterisks in Tables 1-15 as also found by the presented inventors to be dysregulated in MS spinal cords, may be used as targets in combination with one or more of the genes from Tables 1-15.

The inventors also found, quite strikingly, that the CD18 (probe set X64072, also represented by accession number M15395) subunit of lymphocyte function antigen-1 (LFA-1) and of CR3 and CR4 complement, is highly upregulated in all MS samples (including samples with minimal or no inflammation by histological criteria). CD18 plays a role in immune cell activation, cell-cell contacts and as a mediator of phagocytosis. Bowen *et al.* (1998) reported a Phase I study using humanized monoclonal antibodies against CD18 protein in MS patients. In addition, Yusuf-Makagiansar *et al.* (2002) proposed the use of antibodies, peptides and small molecules against CD18 protein to treat autoimmune diseases and inflammation. The present inventors intention, based on striking findings of CD18 mRNA elevation in MS spinal cords, is to target the expression of CD18 mRNA, not protein, in MS central nervous system tissues using technologies such as antisense constructs, RNA interference and other methods described further below.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1 - Kernel density estimate based on five ratios.

FIG. 2A & 2B - Kernel density estimate and histogram of ratios with an adjusted bandwidth.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

In autoimmune diseases, activated T and B cells are hypothesized to clonally expand (*i.e.*, proliferate into multiple daughter cells) and lead to tissue destruction, via infiltration of target tissues with direct cytotoxicity and/or release of harming soluble factors or antibodies. Macrophages are also important mediators of tissue damage. MS is widely considered an autoimmune disease, but there is significant controversy about the key molecules that participate in such process. It also is a heterogeneous disease, and within a single patient, one finds different degrees (and localization in anatomical regions) of demyelination, inflammation and degeneration. The inventors thus examined post-mortem spinal cords via histopathology techniques to determine what type of multiple sclerosis lesions they were working with. Using DNA microarrays, they then determined (by comparing each sample to the average of normal spinal cord samples) the gene expression changes that were unique to each type of MS lesion.

The results reveal that histopathologically different MS spinal cord lesions also exhibit distinct gene expression changes. Thus, gene lists, as set forth in the Tables below, result from the analysis of: (Table 1) MS spinal cord gray matter from a sample with minimal to no inflammation; (Table 2) MS spinal cord gray matter from a sample with lymphocytic inflammation, demyelination and axonal loss; (Table 3) MS spinal cord gray matter from a sample characterized by inflammation by lymphocytes and macrophages, and demyelination; (4) MS spinal cord gray matter from a sample with axonal loss; (Table 5) MS spinal cord white

matter from a sample with minimal to no inflammation; (Table 6) MS spinal cord white matter from a sample with lymphocytic inflammation, demyelination and axonal loss; (Table 7) MS spinal cord white matter from a sample with inflammation by macrophages and demyelination; (Table 8) MS spinal cord white matter from a sample with inflammation by macrophages and lymphocytes and demyelination; and (Table 9) MS spinal cord white matter from a sample with axonal loss. In addition, the inventors provide tables of genes altered in (Table 10) a comparison of the group containing all MS spinal cord gray matter specimens against the group containing all normal gray matter specimens, and (Table 11) a comparison of the group containing all MS spinal cord white matter specimens against the group containing all normal white matter specimens. Also, genes altered commonly across all tables for gray matter (Table 12), white matter (Table 13), and gray & white matter (Table 14) are provided. Table 15 lists genes commonly altered across all comparisons of MS spinal cord white matter characterized by inflammation and demyelination, against normal spinal cord white matter tissues. Table 16, 17 and 18 list genes previously reported to be altered in MS brain tissues by, respectively, Lock *et al.* (2002) (indicated by one asterisk next to a gene identifier in Tables 1-15), Chabas *et al.* (2001) (indicated by two asterisks next to a gene identifier in Tables 1-15), and Whitney *et al.* (1999) (indicated by three asterisks next to a gene identifier in Tables 1-15), and also found by the inventors to be altered (*i.e.*, coregulated and commonly shared) in MS spinal cord tissues. These genes are claimed as targets of treatment only in combination with other genes provided in the inventors' lists (and not in combination with other genes from lists by Lock *et al.* (2002), Chabas *et al.* (2001), or Whitney *et al.* (1999)).

I. Multiple Sclerosis

Multiple Sclerosis (MS) is one of the most common diseases of the central nervous system (brain and spinal cord). It is an inflammatory condition associated with demyelination, or loss of the myelin sheath. Myelin, a fatty material that insulates nerves, acts as insulator in allowing nerves to transmit impulses from one point to another. In MS, the loss of myelin is accompanied by a disruption in the ability of the nerves to conduct electrical impulses to and from the brain and this produces the various symptoms of MS, such as impairments in vision, muscle coordination, strength, sensation, speech and swallowing, bladder control, sexuality and cognitive function. The plaques or lesions where myelin is lost appear as hardened, scar-like

areas. These scars appear at different times and in different areas of the brain and spinal cord, hence the term "multiple" sclerosis, literally meaning many scars.

Currently, there is no single laboratory test, symptom, or physical finding that provides a conclusive diagnosis of MS. To complicate matters, symptoms of MS can easily be confused with a wide variety of other diseases such as acute disseminated encephalomyelitis, Lyme disease, HIV-associated myelopathy, HTLV-I-associated myelopathy, neurosyphilis, progressive multifocal leukoencephalopathy, systemic lupus erythematosus, polyarteritis nodosa, Sjögren's syndrome, Behçet's disease, sarcoidosis, paraneoplastic syndromes, subacute combined degeneration of cord, subacute myelo-optic neuropathy, adrenomyeloneuropathy, spinocerebellar syndromes, hereditary spastic paraparesis/primary lateral sclerosis, strokes, tumors, arteriovenous malformations, arachnoid cysts, Arnold-Chiari malformations, and cervical spondylosis. Consequently, the diagnosis of MS must be made by a process that demonstrates findings that are consistent with MS, and also rules out other causes.

Generally, the diagnosis of MS relies on two criteria. First, there must have been two attacks at least one month apart. An attack, also known as an exacerbation, flare, or relapse, is a sudden appearance of or worsening of an MS symptom or symptoms which lasts at least 24 hours. Second, there must be more than one area of damage to central nervous system myelin sheath. Damage to sheath must have occurred at more than one point in time and not have been caused by any other disease that can cause demyelination or similar neurologic symptoms. MRI (magnetic resonance imaging) currently is the preferred method of imaging the brain to detect the presence of plaques or scarring caused by MS.

The diagnosis of MS cannot be made, however, solely on the basis of MRI. Other diseases can cause comparable lesions in the brain that resemble those caused by MS. Furthermore, the appearance of brain lesions by MRI can be quite heterogeneous in different patients, even resembling brain or spinal cord tumors in some. In addition, a normal MRI scan does not rule out a diagnosis of MS, as a small number of patients with confirmed MS do not show any lesions in the brain on MRI. These individuals often have spinal cord lesions or lesions which cannot be detected by MRI. As a result, it is critical that a thorough clinical exam also include a patient history and functional testing. This should cover mental, emotional, and language functions, movement and coordination, vision, balance, and the functions of the five senses. Sex, birthplace, family history, and age of the person when symptoms first began are

also important considerations. Other tests, including evoked potentials (electrical diagnostic studies that may reveal delays in central nervous system conduction times), cerebrospinal fluid (seeking the presence of clonally-expanded immunoglobulin genes, referred to as oligoclonal bands), and blood (to rule out other causes), may be required in certain cases.

II. MS-Related Genes

In the following pages, the applicants set forth gene targets that may be targeted with therapies for MS. Also included are the particular probes utilized to identify these targets.

In the following tables, a positive value or a plus (+) sign for a $\log_{10}$(ratio)-fold change value, or next to a probe set or gene name, indicates higher expression observed in patients with MS, as compared to healthy individuals. A negative value or a minus (-) sign for a $\log_{10}$(ratio)-fold change value, or next to a probe set or gene name indicates lower expression observed in patients with MS, as compared to healthy individuals.

The inventors provide herein gene lists of altered mRNA transcripts in individual comparisons of gray or white matter tissue samples derived from MS spinal cord against normal spinal cord tissues (Tables 1-9). As stated, the inventors also provide tables of genes altered in a comparison of the entire group containing all MS spinal cord gray matter specimens against the entire group containing normal gray matter specimens (Table 10), and a comparison of the entire group containing all MS spinal cord white matter specimens against the entire group containing normal white matter specimens (Table 11). Finally, the inventors have identified genes that were dysregulated in each list from Tables 1-9, that had a significance of $p<0.05$. Then, a set of common genes that appeared in all gray/white lists was searched and means of $\log_{10}$-fold changes, and p values calculated. Only 5 commonly dysregulated genes were identified in the MS gray matter comparison lists (shown as Table 12), while 23 dysregulated genes were commonly found in the MS white matter lists (shown as Table 13). Then, using the same method, another set of common genes across all lists (both gray and white) was also identified (shown as Table 14). Finally, since MS disease activity is characterized by inflammation and demyelination, a list of common genes shared by three individual comparisons of MS spinal cord white matter samples (all characterized by inflammation and demyelination) against normal spinal cord white matter samples was generated (Table 15). Finally, Tables 16, 17 and 18 show MS spinal cord tissue genes from the present invention that are commonly regulated and shared

with the list of genes altered in MS tissues by Lock *et al.* (2002), Chabas *et al.* (2001), and Whitney *et al.* (1999). These genes are also shown by asterisk(s) preceding the probe set number in Tables 1-15, as follows: shared with the report by Lock *et al.* (one asterisk, Table 16), shared with the report by Chabas *et al.* (two asterisks, Table 17), and shared with the report by Whitney *et al.* (three asterisks, Table 18). The numbers under "Probe Sets" represent the GenBank accession numbers or, in some instances, an identifier provided by Affymetrix.

TABLE 1. Gene targets in MS spinal cord gray matter from a sample with minimal to no histological inflammation.

Probe Set	Gene description	log10 (ratio) fold change
M77829	Channel-like integral membrane prot (CHIP28); Also: S73482	2.1973319000
X95406	Cyclin E	-2.4820424000
U09937	Urokinase-type plasminogen activator receptor; Also: X51675	-2.4221999000
M25280	Lymph node homing receptor	2.0461048000
*X64072	CD18; Also: M15395	2.0293838000
M21305	Alpha satellite and satellite 3 junction DNA sequence	-2.2956496000
M68864	ORF	-2.1876265000
M64788	GTPase activating protein (rap1GAP)	1.9611837000
*M87789	Hybridoma H210 anti-hepatitis A IgG V, C, CDR regions	1.9385197000
U78793	Folate receptor alpha (hFR)/U78793	-2.1603560000
D55696	Cysteine protease	1.9194646000
U02031	Sterol regulatory element binding protein-2	1.9049812000
M98045	Folylpolyglutamate synthetase	-2.1298107000
X57351	1-8D from interferon-inducible family	-2.1186367000
D86971	KIAA0217	1.8382249000
M37457	Na+,K+ -ATPase catalytic subunit alpha-III isoform	1.8061800000
M37755	Pregnancy-specific beta-1-glycoprotein PSGGA	-2.0861373000
X53414	Peroxisomal L-alanine:glyoxylate aminotransferase	-2.0852014000
J04501	Muscle glycogen synthase	1.8014037000
D45906	LIMK-2	-2.0813473000
U60800	Semaphorin (CD100)	1.7899331000
Z84718	DNA on chromosome 22q11.2-qter contains GSTT1-2	1.7710628000
M13207	Granulocyte-macrophage colony-stimulating factor (CSF1)	-2.0635210000
M97252	Kallmann syndrome (KAL)	1.7542944000
U39573	Salivary peroxidase	-2.0552349000
J03600	Lipoxygenase	-2.0488301000
U56816	Kinase Myt1 (Myt1)	-2.0437060000
X17360	HOX 5.1 protein	1.7295697000
Z19002	PLZF kruppel-like zinc finger protein	-2.0348289000
U70732	Glutamate pyruvate transaminase (GPT)	1.7155044000
L02648	(clone V6) transcobalamin II (TCN2)	-2.0310043000
M16707	Histone H4; clone FO108	-2.0251522000
L14812	Retinoblastoma related protein (p107)	-2.0221189000
U73799	Dynactin/U73799	1.6954817000
D28383	ATP synthase B chain	1.6825045000

D50550	LLGL	1.6771760000
M95929	Homeobox protein (PHOX1)	1.6766936000
HG1019-HT1019	Serine Kinase Psk-H1	-2.0052342000
U91327	Chromosome 12p15 BAC clone CIT987SK-99D8 sequence	1.6707096000
M64231	Spermidine synthase	-1.9982048000
U79725	A33 antigen precursor	-2.0023281000
D16583	L-histidine decarboxylase	1.6622855000
U68723	Checkpoint suppressor 1	1.6419879000
U94747	WD repeat protein HAN11/U94747	1.6329632000
U49089	Neuroendocrine-dlg (NE-dlg)	-1.9643186000
U22970	16-Jun (interferon-inducible peptide precursor)	-1.9576671000
X86681	Nucleolar protein HNP36	-1.9585042000
HG2147-HT2217	Mucin 3, Intestinal/M55405	-1.9540012000
X14474	Microtubule-associated tau protein	1.5998831000
D55638	B-cell pseudoautosomal boundary-like sequence	-1.9438653000
M58597	ELAM-1 ligand fucosyltransferase (ELFT)	-1.9472499000
U37519	Aldehyde dehydrogenase (ALDH8)	-1.9341827000
HG651-HT5209	Adducin, Alpha Subunit; Also: Z68280_2, HG651-HT4201	1.5820634000
M13928	X64467_rna1 and others	1.5757650000
M63573	Secreted cyclophilin-like protein (SCYLP)	1.5763414000
U48861	Beta 4 nicotinic acetylcholine receptor subunit	1.5711263000
M12125	Fibroblast muscle-type tropomyosin	-1.9227255000
Z80780	H2B/h/Z80780	1.5641730000
D84454	UDP-galactose translocator	1.5618030000
X96783	Syt V	1.5599066000
X13810	OTF-2 lymphoid-specific transcription factor; Also: M36542	-1.9130850000
X52611	Transcription factor AP-2; Also: HG2465-HT4871, M36711	-1.9158613000
AF000545	Putative purinergic receptor P2Y10	-1.9043097000
L35240	Enigma	1.5440680000
X81420	hHKb1 protein	1.5432976000
D28532	Renal Na+-dependent phosphate cotransporter	-1.8974209000
X63692	DNA (cytosin-5)-methyltransferase	1.5308398000
J05448	RNA polymerase subunit hRPB 33	1.5199493000
U31628	Interleukin-15 receptor alpha chain precursor (IL15RA)	1.5214458000
D43968	AML1b protein	-1.8803133000
M13232	Factor VII serine protease precursor; Also: J02933	-1.8815986000
U57450	EPC-1	-1.8814560000
U29091	Selenium-binding protein (hSBP)/U29091	1.5158738000
Y07755	S100A2	-1.8752784000
X16667	HOX2G from the Hox2 locus	-1.8693784000
HG3033-HT3194	Spliceosomal protein Sap 62	1.5048795000
X52213	Itk; Also: D16105	1.5037907000
X01038	Fetal apolipoprot AI precursor; Also: X07496	-1.8629658000
U64197	Chemokine exodus	-1.8589881000
HG2709-HT2805	Serine/Threonine Kinase	1.4913617000
D29642	KIAA0053	1.4694538000
L11708	17 beta hydroxysteroid dehydrogenase type 2	-1.8364032000
D38502	PMS4 (yeast PMS1 homolog)	1.4631461000
*M85220	Heavy chain disease IgA chain CH3 region	1.4556061000
M60299	Alpha-1 collagen type II s 1 2 and 3	-1.8246952000

M73481	Gastrin releasing peptide receptor (GRPR)	-1.8188030000
D26350	Type 2 inositol 1 4 5-trisphosphate receptor	1.4471580000
X90840	Axonal transporter of synaptic vesicles	-1.8153287000
D59253	NCBP interacting protein 1	1.4369573000
X17651	Myf-4 myogenic determination factor	1.4310639000
M95178	Non-muscle alpha-actinin	1.4240645000
L32866	Effector cell protease receptor-1 (EPR-1)	-1.8044802000
X87871	Hepatocyte nuclear factor 4b; Also: X87870, Z49825	-1.8050759000
HG2510-HT2606	Ras-Specific Guanine Nucleotide-Releasing Factor	1.4210614000
M60298	Erythrocyte membrane protein band 42 (EPB42)	1.4132998000
AF003743	Delayed rectifier potassium channel (KVLQT1-Iso5)	-1.7940211000
U07139	Voltage-gated calcium channel beta subunit	1.4040622000
U33429	K+ channel beta 2 subunit	1.4052248000
L00205	K6b epidermal keratin type II	-1.7875490000
U04847	Ini1	-1.7896688000
U58090	Hs-cul-4A	1.3944517000
U07919	Aldehyde dehydrogenase 6	-1.7871717000
X59798	PRAD1 cyclin	1.3906515000
U78190	GTP cyclohydrolase I feedback regulatory protein	-1.7774268000
D79998	KIAA0176	-1.7700231000
D82344	NBPhox	-1.7704838000
HG919-HT919	Dna Polymerase Epsilon Catalytic Subunit	-1.7714956000
U03911	Mutator (hMSH2)	1.3594190000
U24169	JTV-1 (JTV-1)	1.3614459000
U71364	Serine protase inhibitor (P19)	1.3598355000
S79781	WT1/S79781	-1.7641855000
M31606	Phosphorylase kinase (PSK-C3)	1.3473300000
M95740	Alpha-L-iduronidase	1.3443923000
M27492	Interleukin 1 receptor	-1.7547305000
AD000092	RAD23A homolog	1.3262746000
Y08613	Nup88/Y08613	-1.7490596000
M59820	Granulocyte colony-stimulating factor receptor (CSF3R)	1.3031961000
L04751	Cytochrome p-450 4A (CYP4A)	-1.7450748000
U28281	Secretin receptor	-1.7464396000
X63380	RSRFR2	1.3004888000
U13737	Cysteine protease CPP32 isom alpha	-1.7422340000
M80647	Thromboxane synthase	1.2811352000
X54871	Ras-related protein Rab5b	1.2810334000
X14445	Int-2 protooncogene	-1.7359979000
HG1996-HT2044	Guanine Nucleotide-Binding protein Rap2	1.2741578000
M95809	Basic TRANSCRIPTION FACTOR 62kD subunit (BTF2)	1.2684286000
D43772	GRB-7 SH2 domain	-1.7320317000
M12886	T-cell receptor active beta-chain	-1.7301764000
M18700	D00306, M16630, M18692	-1.7273379000
U49974	Mariner2 transposable element, complete consensus/U49974	-1.7266253000
HG3748-HT4018	Basic Transcription Factor 44 Kda Subunit	1.2504200000
AF015950	Telomerase reverse transcriptase	1.2348010000
HG172-HT3924	Spermidine/Spermine N1-Acetyltransferase	-1.7147488000
HG4749-HT5197	Carnitine Calcium-Binding protein Mitochondrial	-1.7155856000
M55905	Mitochondrial NAD(P)+ dependent malic enzyme	1.2188888000
U82987	Bcl-2 binding component 3 (bbc3)	1.2105620000

M21984	(clone PWHTnT16) skeletal muscle Troponin T	-1.7104347000
U27333	Alpha (1,3) fucosyltransferase (FUT6), major transcript I	-1.7091639000
X52228	Secreted epithelial tumour mucin antigen	-1.7084421000
U11313	Sterol carrier protein-X/sterol carrier protein-2 (SCP-X/SCP-2)	1.2041200000
Y08766	Splicing factor, SF1-Bo isoform; Also: L49380	1.2043797000
Z38133	Myosin; Also: M36769	1.2066376000
X06389	Synaptophysin (p38)	1.1958997000
***J05037	Serine dehydratase	1.1836070000
U66619	SWI/SNF complex 60 KDa subunit (BAF60c)	1.1869136000
AB000462	SH3 binding RES4-23A	-1.6994041000
M34344	Platelet glycoprotein IIb (GPIIb)	-1.6981938000
U03399	T-complex protein 10A (TCP10A)	-1.6989700000
X52599	Beta nerve growth factor	-1.6989700000
M14159	T-cell receptor beta-chain J2.1	-1.6935071000
HG880-HT880	MUC6	-1.6893089000
L27080	Melanocortin 5 receptor (MC5R)	-1.6898081000
X53795	R2 inducible membrane protein	-1.6877853000
J05459	Glutathione transferase M3 (GSTM3)	1.1278244000
M14091	Thyroxine-binding globulin	-1.6859655000
U01157	Glucagon-like peptide-1 receptor with CA dinucleotide repeat	1.1080076000
M74542	Aldehyde dehydrogenase type III (ALDHIII)	-1.6798819000
D28423	Pre-splicing factor SRp20	1.1074088000
X97748	PTX3/X97748; Also: M31166	1.0958364000
M55621	N-acetylglucosaminyltransferase I (GlcNAc-TI)	-1.6770363000
Y07829	RING protein	-1.6729056000
Y09561	P2X7 receptor	1.0883800000
S83325	Aspartyl(asparaginyl)beta-hydroxylase; Also: U03109	1.0849797000
D50920	KIAA0130	-1.6678030000
Y10262	EYA3/Y10262; Also: U81602	-1.6676864000
U80457	TRANSCRIPTION FACTOR SIM2 short form	1.0646428000
L41351	Prostasin	-1.6632296000
J03068	DNF1552 (lung)	1.0594372000
U62433	Nicotinic acetylcholine receptor alpha4 subunit precursor	1.0592429000
L76528	Presenilin 1 (PS1; S182); Also: L76517	1.0524293000
L38933	Putative with an open reading frame	-1.6565773000
S82472	Polymerase beta/S82472	-1.6539357000
M14949	R-ras	1.0389477000
U46746	Dystrobrevin-epsilon; Also: U46744	1.0359475000
X78992	ERF-2	1.0341524000
X76105	DAP-1	1.0298785000
L03840	Fibroblast growth factor receptor 4 (FGFR4); Also: X57205	-1.6517624000
M25077	SS-A/Ro ribonucleoprot autoantigen 60 kd subunit	1.0221579000
X99479	NK receptor, clone 12.11C-Also Similar To: X93596, L76672	-1.6450537000
D13168	Endothelin-B receptor	1.0139885000
HG511-HT511	Ras Inhibitor Inf	1.0134230000
L13698	Growth-arrest-specific protein (gas)	1.0174481000
*U21090	DNA polymerase delta small subunit	1.0132654000
U36448	Ca2+-dependent activator protein secretion	1.0153598000
U82979	Ig-like transcript-3	-1.6332159000
L07592	Peroxisome proliferator activated receptor	-1.6308091000
U15932	Dual-specificity protein phosphatase	-1.6301735000

U32674	Orphan receptor GPR9 (GPR9); Also: X95876	-1.6318241000
X68090	Fc-gamma-RIIA IgG Fc receptor class IIA/X68090	-1.6294096000
D31764	KIAA0064	0.9738912400
M27543	Guanine nucleotide-binding protein (Gi) alpha subunit	0.9751461800
Z11695	40 kDa protein kinase related to rat ERK2	0.9731278500
D31886	KIAA0066	0.9686520200
HG3985-HT4255	Cpg-Enriched Dna Clone E04	-1.6245399000
D10495	Protein kinase C delta-type	0.9660821500
AB000896	Cadherin FIB2	-1.6193542000
U32581	Lambda/iota-prot kinase C-interacting protein	-1.6184404000
U63090	Gal beta-13 GalNAc alpha-23 sialyltransferase (ST3Gal II)	-1.6209873000
*D10704	Choline kinase	0.9532953000
D90359	CCG1	0.9501715500
D29675	iNOS	-1.6131809000
M63904	G-alpha 16 protein	-1.6134650000
D80009	KIAA0187	0.9330532100
Y10260	EYA1	-1.6079909000
Z80345	SCAD; Also: M26393	-1.6091941000
U49188	Placenta (Diff33)	0.9315474000
U23430	Cholecystokinin type A receptor (CCK-A); Also: L19315	0.9255532700
M15465	Pyruvate kinase type L; Also: D13243	-1.6032797000
U17077	BENE	-1.6035503000
U41344	Prolargin (PRELP)	-1.6028735000
Y08836	HRX-like protein/Y08836	-1.6028735000
L21993	Adenylyl cyclase	0.9201585600
L37127	(clone mf18) RNA polymerase II	0.9208968900
U89916	Putative OSP like protein	0.9140545300
U55054	K-Cl cotransporter (hKCC1)	0.9122979900
L38969	Thrombospondin 3 (THBS3)	-1.6019243000
HG3517-HT3711	Alpha-1-Antitrypsin	-1.5969543000
U08021	Nicotinamide N-methyltransferase (NNMT)	-1.5934245000
U82613	DNA-binding protein ABP/ZF	-1.5942544000
X66141	Cardiac ventricular myosin light chain-2	-1.5938900000
X78687	G9 encoding sialidase	-1.5934139000
M81182	Peroxisomal 70 kD membrane protein; Also: X83467_rna1	0.8950389800
U09646	Carnitine palmitoyltransferase II precursor (CPT1)	0.8888069700
*U64573	Connexin43 gap junction protein (connexin43)/U64573	0.8848286700
U18237	ATP-binding cassette protein 06B09 clone	-1.5917600000
X99720	TPRC	0.8798514200
Z46632	HSPDE4C1 3 ,5 -cyclic AMP phosphodiesterase	0.8815503100
S81294	DCC=deleted in colorectal cancer/S81294	-1.5848963000
X77307	5-HT2B serotonin receptor	-1.5841898000
X66362	PCTAIRE-3 serine/threonine protein kinase	0.8690051700
D42053	KIAA0091	0.8599566400
U35139	NECDIN related protein	0.8591271000
U93049	SLP-76 associated protein	0.8613913500
D43947	KIAA0100	0.8530723400
M13903	Involucrin	0.8571154000
M29277	Isolate JuSo MUC18 glycoprot (3 variant); Also: M28882	0.8570771000
D79989	KIAA0167	-1.5764853000
U78876	MEK kinase 3	-1.5733068000

Z83805	Axonemal dynein heavy chain (ID hdhc8)/Z83805	-1.5731618000
U22028	Cytochrome P450 (CYP2A13)	0.8496834500
D87433	KIAA0246	-1.5683484000
U40002	Hormone-sensitive lipase testicular isoform; Also: L11706	-1.5721452000

TABLE 2. Gene targets in MS spinal cord gray matter from a sample with lymphocytic inflammation, demyelination and axonal loss.

Probe set	Gene description	log10 (ratio) fold change
*M87789	Anti-hepatitis A IgG V, C, CDR regions; Also: J00221_2	3.1221503000
Y00067	Neurofilament subunit M (NF-M)	-3.0995382000
D13643	KIAA0018	-3.0496210000
*M63438	Ig rearranged gamma chain , V-J-C region; Also: X96754	2.6660416000
L10678	Profilin II	-2.6086865000
*U62317	Hypothetical protein 384D8_7	2.2480959000
M22538	Mitochondrial NADH-ubiquinone reductase 24Kd subunit	-2.2507938000
X99657	Protein containing SH3 domain SH3GL2	2.2324879000
X98225	Gastrin-binding protein/X98225	2.2077690000
L07597	Ribosomal protein S6 kinase 2 (RPS6KA2)	2.2060088000
D13705	Fatty acids omega-hydroxylase (cytochrome P-450HKV)	-2.4579765000
L14565	Peripherin (PRPH) s 1-9	-2.4614422000
U57341	Neurofilament triplet L protein/U57341	-2.4386017000
U60644	HU-K4	-2.4171186000
Y00757	Polypeptide 7B2	-2.3941670000
D50550	LLGL	2.1022931000
U92457	Metabotropic glutamate receptor 4; Also: X80818	2.1004650000
D63484	KIAA0150	2.0939467000
HG3033-HT3194	Spliceosomal protein Sap 62	2.0822352000
M27749	Ig-related 14.1 protein	2.0722499000
M22632	Mitochondrial aspartate aminotransferase	-2.3186893000
X87870	Hepatocyte nuclear factor 4a	2.0546131000
U18244	Excitatory amino acid transporter 4	2.0463000000
*X00734	Beta-tubulin (5-beta) with ten Alu family members	-2.2901738000
M22976	Cytochrome b5	-2.2794103000
M57609	DNA-binding protein (GLI3)	-2.2654959000
D50663	TCTEL1	-2.2489536000
J05073	Phosphoglycerate mutase (PGAM-M)	1.9672499000
U82987	Bcl-2 binding component 3 (bbc3)	1.9497120000
L35240	Enigma	1.9412629000
S83390	T3 receptor-associating cofactor-1; Also: U37146	1.9278533000
L07738	DHP-sensitive calcium channel gamma subunit (CACNLG)	1.9250541000
D43767	Chemokine	-2.2221635000
L40397	(clone S31i125)	-2.2061848000
M36542	Lymphoid-specific transcription factor; Also: X13810, X13809	-2.2043574000
U11877	Interleukin-8 receptor type B (IL8RB)/U11877	1.8893017000
J00123	Enkephalin	-2.1938895000
X92896	ITBA2 protein	-2.1926490000
X15331	Phosphoribosylpyrophosphate synthetase subunit one	-2.1855067000
Z21488	Contactin	-2.1837679000
U49973	Tigger 1 transposable element	1.8618330000

D16583	L-histidine decarboxylase	1.8518696000
U52969	PEP19 (PCP4)	-2.1730770000
**X05299	(~95%) major centromere autoantigen CENP-B	1.8387444000
X01630	Argininosuccinate synthetase	-2.1602058000
D50402	NRAMP1	1.8214780000
J00220	IGHA1 from Ig germline H-chain G-E-A region A: gamma-3 5	1.8210038000
U16031	TRANSCRIPTION FACTOR IL-4 Stat	1.8178958000
X67325	p27	-2.1546522000
M29927	Ornithine aminotransferase	-2.1375915000
M87860	S-lac lectin L-14-II (LGALS2)	1.7914660000
M58509	FDXR (adrenodoxin reductase); Also: HG2836-HT2962	1.7833611000
L47345	Elongin A	-2.1360464000
M13755	Interferon-induced 17-kDa/15-kDa protein	-2.1340391000
HG3928-HT4198	SFTPA2D	1.7625109000
HG2348-HT2444	Peptide Yy; Also: D13897	1.7609311000
L34587	RNA polymerase II elongation factor SIII p15 subunit	-2.1126469000
X05608	Neurofilament subunit NF-L	-2.1160768000
M95178	Non-muscle alpha-actinin	1.7450748000
D38128	IP prostacyclin receptor	1.7411516000
HG2604-HT2700	Pan-2	1.7415455000
U42408	Ladinin (LAD)	1.7395723000
Z33905	43kD acetylcholine receptor-associated protein (Rapsyn)	1.7335985000
L41143	Expressed pseudo TCTA at t(1;3) translocation site	-2.1054392000
HG4128-HT4398	Anion Exchanger 3 Cardiac Isom	1.7299743000
X64037	RNA polymerase II associated protein RAP74	-2.0997238000
X52638	6-phosphofructo-2-kinase/fructose-26-bisphosphatase	-2.0953001000
U72671	Telencephalin precursor	1.7172543000
D85758	DROER homolog	-2.0905666000
*L26339	Autoantigen	1.7041505000
U50360	Calcium, calmodulin-dependent protein kinase II gamma	-2.0863598000
X53414	Peroxisomal L-alanine:glyoxylate aminotransferase	-2.0852014000
U89336	Notch 4	1.6941903000
U79255	X11 protein	-2.0789097000
X99142	Hair keratin hHb6	-2.0812573000
D14663	KIAA0107	-2.0728011000
X99897	P/Q-type calcium channel alpha1 subunit; Also: U79663	1.6798819000
J00124	50 kDa type I epidermal keratin	-2.0680931000
X04706	Homeobox (clone HHO.c13); Also: X17360	1.6702459000
M13207	Granulocyte-macrophage colony-stimulating factor (CSF1)	-2.0635210000
X02761	Fibronectin (FN precursor); Also: HG3044-HT2527	-2.0637086000
U61734	Protein trafficking protein (S31iii125); Also: L40397	-2.0620176000
D50532	Macrophage lectin 2	1.6536841000
L09708	Complement component 2 (C2) allele b	1.6573649000
M74509	HG4045-HT4315 and others	-2.0537025000
S72487	Orf1 to PD-ECGF/TPorf2 to PD-ECGF/TP	-2.0528382000
X17094	Furin	1.6503075000
*D13988	Rab GDI	-2.0496540000
X59842	PBX2; Also: U89336_2, D28769_1, X80700	-2.0479877000
X02958	Interferon alpha IFN-alpha 6	1.6349808000
U35340	Beta B1-crystallin	1.6263404000

L02648	(clone V6) transcobalamin II (TCN2)	-2.0310043000
U23803	Heterogeneous ribonucleoprotein A0	-2.0311711000
U91316	Acyl-CoA thioester hydrolase	-2.0287237000
M16707	Histone H4; clone FO108	-2.0251522000
M86826	IGF binding protein complex acid-labile subunit a	1.6117233000
X81637	Clathrin light chain b	1.6111921000
U25801	Tax1 binding protein	1.6031444000
M96738	Somatostatin receptor subtype 3 (SSTR3); Also: Z86000	1.5993371000
D49817	Fructose 6-phosphate 2-kinase/fructose 2 6-bisphosphatase	-2.0132587000
U73499	Hepatic nuclear factor 1-alpha (TCF-1-alpha)/U73499	1.5929617000
HG2709-HT2805	Serine/Threonine Kinase	1.5910646000
HG4115-HT4385	Olfactory Receptor Or17-210	1.5899496000
S77893	GPSAT=glycophorin SAT; Also: L31860	1.5831988000
D50913	KIAA0123	-2.0061450000
M33882	p78 protein	-2.0057702000
X77748	Metabotropic glutamate receptor type 3	-2.0060915000
HG3991-HT4261	Cpg-Enriched Dna, Clone E18	1.5809250000
*U62317	Hypothetical protein 384D8_7	1.5818566000
*J03263	Lysosome-associated membrane glycoprotein (lamp A)	-2.0018959000
M81780	SMPD1	1.5735256000
X70070	Neurotensin receptor	1.5770137000
M64925	Palmitoylated erythrocyte membrane protein (MPP1)	-1.9929399000
X07315	PP15 (placental protein 15)	-1.9968399000
U82279	Ig-like transcript 2	1.5717088000
K03021	Tissue plasminogen activator (PLAT)	-1.9892829000
X06956	HALPHA44 alpha-tubulin	-1.9917528000
S69370	PAX3B=transcription factor; Also: S69369	1.5611014000
S52969	Alpha-1.3 fucosyltransferase/FucT-III and Fuct-VI	-1.9849209000
U32645	Myeloid elf-1 like factor (MEF)	1.5563025000
HG2259-HT2348	Tubulin, Alpha 1; Also: X06956	-1.9746844000
M77810	TRANSCRIPTION FACTOR GATA-2	1.5440680000
U01828	Microtubule-associated protein 2 (MAP2)	1.5378191000
*X64072	CD18; Also: M15395	1.5346606000
X77567	InsP3 5-phosphatase; Also: Z31695	1.5360159000
M21574	Platelet-derived growth factor receptor alpha (PDGFRA)	-1.9621325000
U22970	16-Jun (interferon-inducible peptide precursor); Also: U22970	-1.9576671000
U60521	Protease proMch6 (Mch6)	-1.9583249000
D38163	a1(XIX) collagen chain; Also: U09279	1.5232039000
D86549	p97 homologous protein	-1.9537597000
L36983	Dynamin (DNM)	-1.9527319000
S67247	Smooth muscle myosin heavy chain isoform Smemb	1.5204835000
U73799	Dynactin/U73799	1.5198280000
X98258	M-phase phosphoprotein mpp9	1.5211381000
U18671	Stat2	-1.9471273000
U24183	Phosphofructokinase (PFKM); Also: HG1849-HT1878	-1.9432471000
L41939	(clone FBK III 11c) protein-tyrosine kinase (DRT)	1.5047354000
L08069	Heat shock protein E coli DnaJ homolog	-1.9388323000
HG4458-HT4727	Ig Heavy Chain Vdjc Regions	1.4976206000
U46767	Monocyte chemoattractant protein-4 precursor (MCP-4)	1.5006024000
U17886	Succinate dehydrogenase iron-protein subunit (sdhB)	-1.9363881000
S71018	Cyclophilin C	1.4892552000

D14874	Adrenomedullin	-1.9296743000
M62843	Antigen of paraneoplastic sensory neuronopathy patients	-1.9305033000
U28488	Putative G protein-coupled receptor (AZ3B); Also: U62027	1.4864470000
X82324	Brain 4	1.4828736000
X52008	Strychnine binding subunit of inhibitory glycine receptor	-1.9199275000
*M35999	Platelet glycoprotein IIIa (GPIIIa)	1.4727564000
U08316	Insulin-stimulated protein kinase 1 (ISPK-1)	-1.9153998000
X13810	OTF-2 lymphoid-specific transcription factor; Also: M36542	-1.9130850000
M89470	Paired-box protein (PAX2); Also: L25597	-1.9122221000
X03072	Int-1 mammary oncogene	-1.9080827000
X66363	PCTAIRE-1 serine/threonine protein kinase	-1.9106244000
L14848	MHC class I-related protein; Also: X91625, U65416, X92841	1.4664804000
X97748	PTX3/X97748; Also: M31166	1.4629523000
M21056	Pancreatic phospholipase A-2 (PLA-2)	1.4616772000
M92934	Connective tissue growth factor	-1.9045194000
U07620	MAP kinase	-1.9057284000
U41668	Deoxyguanosine kinase	-1.9062003000
U95006	D9 splice variant A	-1.9062677000
M60891	Uroporphyrinogen decarboxylase (URO-D) /M60891	1.4528033000
M86406	Skeletal muscle alpha 2 actinin	-1.8953535000
*Y12711	Putative progesterone binding protein	-1.8947313000
X15675	pTR7 repetitive sequence/X15675	1.4440448000
Z46788	Cylicin II	1.4471580000
M99438	Transducin-like enhancer protein (TLE3)	1.4392274000
L78833	Ifp35 from Rho7 vatl and BRCA1	-1.8836614000
M94077	Loricrin	1.4364518000
U62433	Nicotinic acetylcholine receptor alpha4 subunit precursor	1.4370998000
K03183	Chorionic gonadotropin beta subunit	-1.8803276000
M65085	Follicle stimulating hormone receptor	1.4251925000
X80026	B-cam	-1.8752784000
M60459	Erythropoietin receptor	1.4224257000
M64595	Small G protein (Gx)	1.4207806000
U19247	Interferon-gamma receptor alpha chain	-1.8687913000
X78992	ERF-2	1.4167905000
L41147	5-HT6 serotonin receptor	-1.8638257000
X77794	Cyclin G1	-1.8655481000
U64197	Chemokine exodus	-1.8589881000
U81607	Gravin	-1.8604129000
*L25270	XE169	1.4063065000
U72507	40871 sequence	1.4070380000
L16991	Thymidylate kinase (CDC8)	-1.8551404000
L31573	Sulfite oxidase	1.3947839000
L44140	DNL1L from chromosome X region; Also: X90392	1.3935752000
M63573	Secreted cyclophilin-like protein (SCYLP)	1.3953264000
X51804	PMI a putative receptor protein	-1.8500333000
X87176	17-beta-hydroxysteroid dehydrogenase	-1.8495730000
U56833	VHL binding protein-1 (VBP-1)	-1.8445548000
U53174	Cell cycle checkpoint control protein	1.3829171000
D10925	HM145	1.3812916000
M11321	Group-specific component vitamin D-binding protein	1.3820170000
X90999	Glyoxalase II	-1.8350561000

HG1139-HT4910	Fk506-Binding protein	1.3765770000
HG4683-HT5108	Tumor Necrosis Factor Receptor 2 Associated protein Trap3	1.3756148000
M17252	Cytochrome P450c21	1.3773315000
X15954	MBP1; Also: X15422	1.3747483000
U76456	Tissue inhibitor of metalloproteinase 4	1.3694342000
L38487	Estrogen receptor-related protein (hERRa1)	-1.8276358000
AF000234	P2x purinoceptor	1.3626709000
HG4051-HT4321	Choline Acetyltransferase	1.3626709000
M27878	DNA binding protein (HPF2)	1.3645510000
U65011	Preferentially expressed antigen of melanoma (PRAME)	1.3652493000
X52896	Dermal fibroblast elastin; Also: HG2994-HT4851	1.3636120000
Z35278	PEBP2aC1 acute myeloid leukaemia	1.3626709000
X89067	Trpc2 transcript (possible pseudo)	1.3586961000
D78275	Proteasome subunit p42	-1.8189678000
L24804	(p23)	-1.8218409000
M24594	Interferon-inducible 56 Kd protein	-1.8170693000
X90840	Axonal transporter of synaptic vesicles	-1.8153287000
HG4557-HT4962	Small Nuclear Ribonucleoprotein U1, 1snrp	1.3434086000
S76067	CNG2=cyclic nucleotide-gated cation channel/S76067	1.3456620000
D85433	MURR1	-1.8097280000
X12458	P3	1.3414345000
D28383	ATP synthase B chain	1.3369167000
Z84721	DNA from 16p13.3 Contains alpha and zeta globin	-1.8031156000
U80017	Survival motor neuron protein	1.3281136000
D42087	KIAA0118	-1.8007171000
J05582	Pancreatic mucin; Also: J05581	-1.8004593000
L00634	Farnesyl-protein transferase alpha-subunit; Also: L10413	-1.7992544000
S80335	Integrin beta 7 subunit	1.3252515000
U67849	Beta-galactoside alpha26-sialyltransferase (SIAT1)/U67849	1.3200240000
HG2815-HT2931	Myosin, Light Chain/U02629; Also: HG2815-HT1357	-1.7970077000
X80343	p35 regulatory subunit of cdk5 kinase	1.3159703000
L43579	(clone 110298)/L43579; Also: L43575	-1.7886985000
M21005	Migration inhibitory factor-related protein 8 (MRP8)	-1.7900211000
S74683	ADP-ribosyltransferase	-1.7919537000
U07000	BCR (unknown) from breakpoint cluster region (BCR)	-1.7916029000
U10117	Endothelial-monocyte activating polypeptide II	-1.7917783000
X59417	PROS-27	-1.7922165000
*HG2730-HT2828	Fibrinogen, A Alpha Polypeptide; Also: M58569	1.3053514000
X07203	CD20 receptor (S7)	1.3053088000
D86956	KIAA0201	-1.7865740000
U07151	GTP binding protein (ARL3)	-1.7839036000
U73167	H_LUCA146	-1.7841714000
M76180	Aromatic amino acid decarboxylase (ddc)	1.3010300000
Z69923	DNA sequence from Huntington's Disease Region	1.3015718000
D80009	KIAA0187	1.2953744000
M34041	Alpha-2-adrenergic receptor (alpha-2 c2)	-1.7816656000
M96956	(clone CR-3) teratocarcinoma-derived growth factor 3 TDGF3	1.2922561000
M59820	Granulocyte colony-stimulating factor receptor (CSF3R)	1.2833012000
HG4258-HT4528	Kinase Inhibitor P27kip1 Cyclin-Dependent	-1.7678976000
X57129	H12 histone H1	1.2764618000

*HG1595-HT4788	Heterogeneous Nuclear Ribonucleoprotein I; Also: HG1595-HT4789, X66975	1.2717876000
M32334	Intercellular adhesion molecule 2 (ICAM-2)	-1.7634280000
M98343	Amplaxin (EMS1)	-1.7631471000
X69950	DNA sequence for Wilms tumor; Also: M60614	-1.7625848000
AC002450	BAC clone GS244B22/7q21-q22/AC002450	1.2669762000
Z46632	HSPDE4C1 3,5 -cyclic AMP phosphodiesterase	1.2671717000

TABLE 3. Gene targets in MS spinal cord gray matter from a sample characterized by inflammation by lymphocytes and macrophages, and demyelination.

Probe set	Gene description	log10 (ratio) fold change
X05608	Neurofilament subunit NF-L	-2.9853086000
*M87789	Anti-hepatitis A IgG V, C, CDR regions; Also: J00221_2	3.4707705000
*M63438	Ig rearranged gamma chain , V-J-C region; Also: X96754	3.4656016000
L76200	Guanylate kinase (GUK1)	-2.5051160000
M34516	Omega light chain protein 14.1 (Ig lambda chain related)	2.5219506000
S68616	Na+/H+ exchanger NHE-1 isom	-2.4902746000
L11672	Kruppel related zinc finger protein (HTF10)	-2.4847446000
L44140	DNL1L from chromosome X region; Also: X90392	2.2062455000
U57341	Neurofilament triplet L protein/U57341	-2.4386017000
*X13334	CD14 myeloid cell-specific leucine-rich glycoprotein	2.1191968000
M62505	C5a anaphylatoxin receptor	2.0890128000
L28821	Alpha mannosidase II isozyme	-2.3860975000
D50402	NRAMP1	2.0422244000
*X64072	CD18; Also: M15395	2.0330818000
M27826	Endogenous retroviral protease	-2.3628828000
Z22548	Thiol-specific antioxidant protein	-2.3496417000
HG3991-HT4261	Cpg-Enriched Dna, Clone E18	2.0112320000
U28488	Putative G protein-coupled receptor (AZ3B); Also: U62027	1.9889735000
M80397	DNA polymerase delta catalytic subunit; Also: M81735	-2.3239221000
U09210	Vesicular acetylcholine transporter	-2.3253617000
J04469	Mitochondrial creatine kinase (CKMT)	-2.3121244000
U77643	K12 protein precursor	1.9392946000
U43916	Tumor-associated membrane protein homolog (TMP)	1.9347509000
M27161	MHC class I CD8 alpha-chain (Leu-2/T8)	-2.2965281000
*X00734	Beta-tubulin (5-beta) with ten Alu family members	-2.2901738000
D00654	Enteric smooth muscle gamma-actin	1.9127421000
HG3286-HT3463	Crystallin Alpha A	-2.2734643000
L13266	N-methyl-d-aspartate receptor (NR1-1)	-2.2750809000
D49357	S-adenosylmethionine synthetase	1.8856319000
X84213	BAK BCl-2 homolog; Also: U16811, U23765	1.8714562000
U76366	Treacher Collins syndrome (TCOF1); Also: U84665, U40847	-2.2445863000
M77829	Channel-like integral membrane protein (CHIP28); Also: S73482	1.8463279000
D63478	KIAA0144	-2.2079372000
U93049	SLP-76 associated protein	1.8208888000
M36542	Lymphoid-specific transcription factor; Also: X13810, X13809	-2.2043574000
HG3731-HT4001	Ig Heavy Chain, Vdjrc Regions L23566	1.8025389000
M95178	Non-muscle alpha-actinin	1.7921114000
X98225	Gastrin-binding protein/X98225	1.7825443000

X15306	NF-H 1	-2.1689075000
*M24766	Alpha-2 collagen type IV (COL4A2); Also: X05610	1.7779340000
X07834	Manganese superoxide dismutase SOD2	1.7802453000
D44466	Proteasome subunit p112	-2.1663931000
Z49254	L23-related	-2.1637203000
U18550	GPR3 G protein-coupled receptor	1.7746994000
J05068	Transcobalamin I	1.7700047000
M59820	Granulocyte colony-stimulating factor receptor (CSF3R)	1.7714405000
U38480	Retinoid X receptor-gamma	-2.1610684000
X87212	Cathepsin C	1.7590364000
HG2036-HT2090	Stimulatory Gdp/Gtp Exchange protein C-Ki-Ras P21/Smg P21	-2.1415673000
Y08409	Spot14	-2.1407044000
L47345	Elongin A	-2.1360464000
U49837	LIM protein MLP	-2.1346153000
M96944	B-cell specific TRANSCRIPTION FACTOR (BSAP)	1.7306208000
M98045	Folylpolyglutamate synthetase	-2.1298107000
D80004	KIAA0182	-2.1272263000
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X70991	MADER	1.7156601000
X64037	RNA polymerase II associated protein RAP74	-2.0997238000
U50360	Calcium, calmodulin-dependent protein kinase II gamma/U50360	-2.0863598000
J05257	Clones MDP4 MDP7 microsomal dipeptidase (MDP)	1.6624745000
U79261	Clone 23959; Also: U62317_rna1	-2.0810321000
X77588	HG3988-HT4258 and others	-2.0753188000
X17094	Furin	1.6512295000
M13207	Granulocyte-macrophage colony-stimulating factor (CSF1)	-2.0635210000
S85963	hIRS-1=rat insulin receptor substrate-1 homolog	1.6198012000
*X57809	Rearranged Ig lambda light chain; Also: S42404	1.6185978000
U49260	Mevalonate pyrophosphate decarboxylase (MPD)	-2.0366788000
D42040	KIAA9001; Also: X62083, M80613	-2.0292924000
U62293	LIMK1 (LIM-kinase1); Also: U63721_rna2 , U63721_rna2	-2.0282153000
HG491-HT491	Fc Receptor Iib3 For Igg, Low Affinity	1.6060050000
HG2797-HT2906	Clathrin, Light Polypeptide B- Also: X81637, HG2797-HT2905	-2.0267375000
M25322	Granule membrane protein-140	-2.0059844000
X06956	HALPHA44 alpha-tubulin	-2.0045900000
D29642	KIAA0053	1.5838220000
Y00970	Acrosin (EC 342110)	1.5839352000
*S82024	SCG10=neuron-specific growth-associated protein	-1.9997722000
D83920	Uterus ficolin-1	1.5799550000
U47621	Nucleolar autoantigen No55	1.5800958000
M85247	Dopamine D1A receptor/M85247	-1.9920009000
U37219	Cyclophilin-like protein CyP-60	-1.9864918000
**X05299	(~95%) major centromere autoantigen CENP-B	1.5698259000
X63380	RSRFR2	1.5688006000
AF002224	E6-AP ubiquitin protein ligase 3A/promoter P1	1.5625902000
HG2348-HT2444	Peptide Yy; Also: D13897_rna2	1.5661874000
HG2259-HT2348	Tubulin, Alpha 1; Also: X06956	-1.9746844000
M36200	Synaptobrevin 1 (SYB1)	-1.9770946000
M13981	Inhibin A-subunit	1.5621968000
D13636	KIAA0011	-1.9620140000
U68031	G protein-coupled receptor (STRL22)/U68031	1.5521813000

Z38133	Myosin; Also: M36769	1.5518470000
M80647	Thromboxane synthase	1.5441298000
X14474	Microtubule-associated tau protein	1.5436335000
X14813	3-oxoacyl-CoA thiolase	-1.9496339000
HG1728-HT1734	CGM1	1.5412047000
L35240	Enigma	1.5380079000
HG1098-HT1098	Cystatin D	1.5345338000
L42176	(clone 353) DRAL	1.5358003000
S66431	RBP2=retinoblastoma binding protein 2	1.5358003000
U58090	Hs-cul-4A	1.5331363000
X51954	UCP1 uncoupling protein/X51954	1.5328482000
HG4593-HT4998	Sodium Channel 1	-1.9391106000
U17886	Succinate dehydrogenase iron-protein subunit (sdhB)	-1.9363881000
U37519	Aldehyde dehydrogenase (ALDH8)	-1.9341827000
D84557	HsMcm6	-1.9302484000
M62843	Antigen in paraneoplastic sensory neuronopathy patients	-1.9305033000
L10377	(clone CTG-B37) sequence; Also: D38529, U23851, D31840	1.5271786000
HG2825-HT2949	Ret Transforming	-1.9244085000
L10717	T cell-specific tyrosine kinase	1.5193028000
M25897	Platelet factor 4 (PF4)	1.5222276000
U85265	Down syndrome critical region 1 (DSCR1) alternative 1	1.5216642000
D10995	Serotonin 1B receptor	-1.9209056000
X52008	Strychnine binding subunit of inhibitory glycine receptor	-1.9199275000
HG3491-HT3685	Zinc Finger protein Zfp-36	1.5150123000
U20647	Zinc finger protein (ZNF151)	-1.9093554000
L77213	Phosphomevalonate kinase	-1.9056610000
S82240	RhoE=26 kda GTPase homolog	1.5021539000
*M74826	Glutamate decarboxylase (GAD-2)	-1.8953535000
*X07109	Protein kinase C (PKC) type beta II	-1.8952153000
HG4490-HT4876	Proline-Rich protein Prb4, Allele	-1.8905607000
HG4051-HT4321	Choline Acetyltransferase	1.4882686000
M21665	Beta-myosin heavy chain; Also: X52889	1.4892253000
X81420	hHKb1 protein	1.4919523000
L23333	Corticotropin releasing factor receptor; Also: X72304	-1.8873359000
D16815	EAR-1r	1.4869969000
M25280	Lymph node homing receptor	1.4825163000
D43968	AML1b protein	-1.8803133000
K03183	Chorionic gonadotropin beta subunit	-1.8803276000
M13232	Factor VII serine protease precursor; Also: J02933	-1.8815986000
U23803	Heterogeneous ribonucleoprotein A0	-1.8788827000
U59736	TRANSCRIPTION FACTOR (NFATcb)	-1.8802368000
L09708	Complement component 2 (C2) allele b	1.4794162000
X78992	ERF-2	1.4819119000
X80026	B-cam	-1.8752784000
Y07755	S100A2	-1.8752784000
HG2709-HT2805	Serine/Threonine Kinase	1.4744348000
L40396	(clone s22i71)	1.4763968000
D83784	KIAA0198	-1.8699647000
L13972	Beta-galactoside alpha-23-sialyltransferase (SIAT4A)	-1.8688648000
X16667	HOX2G from the Hox2 locus	-1.8693784000
U24577	LDL-phospholipase A2	1.4699388000

L41147	5-HT6 serotonin receptor	-1.8659918000
U31929	Orphan nuclear receptor (DAX1); Also: S74720	-1.8651780000
U79271	Clones 23920 and 23921 sequence	1.4633207000
U96131	HPV16 E1 protein binding protein/U96131	-1.8599635000
D59253	NCBP interacting protein 1	1.4611983000
J04102	Erythroblastosis virus onco homolog 2 (ets-2)	1.4614809000
X68149	BLR1 Burkitt's lymphoma receptor 1	1.4621733000
AF001620	Trabecular meshwork-induced glucocorticoid response protein	1.4517097000
S77763	Nuclear factor erythroid 2 isom f=basic leucine zipper protein	-1.8464144000
L20826	I-plastin	-1.8419067000
U60415	bHLH-PAS protein Jap3	1.4420092000
X06389	Synaptophysin (p38)	1.4336098000
X17360	HOX 5.1 protein	1.4333697000
M97496	Guanylin	1.4266739000
S81578	Dioxin-responsive/S81578	1.4274050000
U80017	Survival motor neuron protein	1.4251371000
X67318	Procarboxypeptidase A1	1.4263486000
M60299	Alpha-1 collagen type II s 1 2 and 3/M60299	-1.8246952000
D85939	p97 homolog	1.4219328000
M22403	Blood platelet membrane glycoprotein Ib-alpha (GPIB)	1.4189234000
X99296	RD/X99296	1.4203205000
M73481	Gastrin releasing peptide receptor (GRPR)	-1.8188030000
U53476	Proto-onco Wnt7a	-1.8187206000
D42045	KIAA0086	1.4135512000
M12759	Ig J chain	1.4128674000
S71043	Ig alpha 2=Ig A heavy chain allotype 2; Also: S55735	1.4131120000
X14690	Plasma inter-alpha-trypsin inhibitor heavy chain H(3)	1.4075608000
X74039	Urokinase plasminogen activator receptor	-1.8169866000
X87904	SEP protein	-1.8142476000
X90840	Axonal transporter of synaptic vesicles	-1.8153287000
M63256	Major Yo paraneoplastic antigen (CDR2)	1.4072771000
U20240	C/EBP gamma	1.4061322000
M16707	Histone H4; clone FO108	-1.8076683000
X54871	Ras-related protein Rab5b	1.3981137000
S72493	Keratin=keratin 16 homolog; Also: M28439	-1.8036278000
U68233	Farnesol receptor HRR-1 (HRR-1)	-1.8026027000
X74794	P1-Cdc21	-1.8037791000
X87871	Hepatocyte nuclear factor 4b; Also: X87870, Z49825	-1.8050759000
Z84721	DNA from 16p13.3 Contains alpha and zeta globin	-1.8031156000
M68516	PCI (plasminogen activator inhibitor 3) from protein C inhibitor	1.3888114000
U46746	Dystrobrevin-epsilon; Also: U46744	1.3918125000
S68874	EP3 prostanoid receptor EP3-I; Also: D86096_1, X83858	-1.8020036000
X89211	DNA endogenous retroviral like element/X89211	-1.7982189000
HG3570-HT3773	Protein Phosphatase Inhibitor Homolog	-1.7935634000
X63755	High-sulphur keratin	1.3680604000
L08424	Achaete scute homologous protein (ASH1)	-1.7847064000
D86062	KNP-Ib; Also: U53003	1.3634666000
M95929	Homeobox protein (PHOX1)	1.3627651000
S75313	MJD1=MJD1 protein {CAG repeats}	1.3585874000
X70649	CI1042 of DEAD box protein family	-1.7784226000
Y00757	Polypeptide 7B2	-1.7792698000

D87002	POM121-like 1	1.3552599000
HG2260-HT2349	Duchenne Muscular Dystrophy protein (Dmd); Also: M18533	1.3538201000
M25809	Endomembrane proton pump subunit	-1.7725967000
X62515	Basement membrane heparan sulfate proteoglycan	-1.7758834000
U22662	Nuclear orphan receptor LXR-alpha	1.3447851000
D79998	KIAA0176	-1.7700231000
HG919-HT919	Dna Polymerase Epsilon Catalytic Subunit	-1.7714956000
J05252	Also: M95971	-1.7686381000
U96629	Hereditary multiple exostosis	1.3424227000
M74093	Cyclin	-1.7639892000
S79781	WT1/S79781	-1.7641855000
M55024	Cell surface glycoprotein P3.58;/M55024; Also: M24283	1.3357587000
U09550	Oviductal glycoprotein	1.3283163000
D26561	ORF E7 from papillomavirus 5b genome	-1.7600453000
M97252	Kallmann syndrome (KAL)	1.3249620000
D17516	PACAP receptor	1.3201401000
D49493	Bone morphogenetic protein-3b	1.3221159000
L02867	62 kDa paraneoplastic antigen	-1.7546350000
M34539	FK506-binding protein (FKBP)	-1.7572062000
M17183	Parathyroid hormone-related protein; Also: M24351_3, J03580	1.3152354000
D87937	Alpha(1,2)fucosyltransferase 5	-1.7500260000
D89377	MSX-2	-1.7507012000
U43843	H-neuro-d4 protein	-1.7503155000
D42054	KIAA0092	1.3057652000
M55905	Mitochondrial NAD(P)+ dependent malic enzyme	1.3051620000
U28281	secretin receptor	-1.7464396000
Z34975	LDLC	-1.7474409000
HG3187-HT3366	Tyrosine Phosphatase 1; Also: HG3187-HT3365, U12128	1.3023642000
M27543	Guanine nucleotide-binding protein (Gi) alpha subunit	1.3007215000
U18991	Retinal pigment epithelium-specific 61 kDa protein (RPE65)	1.2986348000
HG4245-HT4515	Khead Family Afx1	1.2941354000
M83652	Complement component properdin; Also: X57748	1.2929203000
HG4234-HT4504	Methylenetetrahydrofolate Reductase	-1.7398689000
Z74792	CCAAT transcription binding factor subunit gamma	-1.7387806000
S66896	Squamous cell carcinoma antigen=serine protease inhibitor	1.2912578000
D17400	6-pyruvoyl-tetrahydropterin synthase	-1.7353993000
Y08134	ASM-like phosphodiesterase 3b	-1.7374908000
D29992	Placental protein 5 (PP5)	1.2797753000
X15088	GNAT1 transducin alpha-chain	1.2820442000
HG1747-HT1764	Proto-Oncogene Met; Also: J02958, U08818	-1.7316895000
M12886	T-cell receptor active beta-chain	-1.7301764000
U07231	G-rich sequence factor-1 (GRSF-1)	-1.7299743000
X17254	TRANSCRIPTION FACTOR Eryf1	-1.7314880000
X77567	InsP3 5-phosphatase; Also: Z31695	1.2761490000
V00535	IFNB 1; Also: J00218_rna1, V00547, M28622, V00534_rna1	1.2694863000
L22454	Nuclear respiratory factor-1 (NRF-1)	-1.7246854000
M18700	D00306, M16630, M18692	-1.7273379000
U79245	Clone 23586 sequence	-1.7266253000
X02404	CGRP from medullary thyroid carcinoma (MTC)	-1.7271344000
Z46376	HK2 hexokinase II	1.2635177000
D14134	RAD51	1.2598327000

U79293	Clone 23948 sequence	1.2617385000
L21998	Intestinal mucin (MUC2)	-1.7202627000
M65062	Insulin-like growth factor binding protein 5 (IGFBP-5)	1.2530956000
U78095	Placental bikunin	-1.7129652000
D10495	Protein kinase C delta-type	1.2435668000
HG3288-HT3465	Xanthine Dehydrogenase	-1.7119126000
M21984	(clone PWHTnT16) skeletal muscle Troponin T	-1.7104347000
U47928	Protein A alternatively spliced m 2 (A-2)	-1.7110687000
X52228	Secreted epithelial tumour mucin antigen	-1.7084421000
X59373	HOX4D a homeobox protein	-1.7115964000
HG2841-HT2969	Albumin, 3; Also: HG2841-HT2970, HG2841-HT2968	1.2377036000
U29589	m3 muscarinic acetylcholine receptor (CHRM3)	1.2402996000

TABLE 4. Gene targets in MS spinal cord gray matter from a sample with axonal loss.

Probe set	Gene description	log10 (ratio) fold change
D26129	RNase A	-2.7780879000
*M87789	Anti-hepatitis A IgG V, C, CDR regions; Also: J00221_2	3.7091911000
*M63438	Ig rearranged gamma chain , V-J-C region; Also: X96754	3.6640039000
L13210	Mac-2 binding protein	-2.6950437000
L16862	G protein-coupled receptor kinase (GRK6)	-2.6041720000
M25280	Lymph node homing receptor	2.0987648000
D49357	S-adenosylmethionine synthetase	2.0759381000
L76200	Guanylate kinase (GUK1)	-2.5051160000
X74570	Gal-beta(1-3/1-4)GlcNAc alpha-23-sialyltransferase	-2.4956310000
S68616	Na+/H+ exchanger NHE-1 isom	-2.4902746000
L44140	DNL1L from chromosome X region; Also: X90392	2.0235817000
L14565	Peripherin (PRPH) s 1-9	-2.4614422000
S76638	p50-NF-kappa B homolog	1.9947998000
HG2709-HT2805	Serine/Threonine Kinase	1.9764875000
X84213	BAK BCl-2 homolog; Also: U16811, U23765	1.9659539000
*X63578	Parvalbumin	-2.3866104000
X14474	Microtubule-associated tau protein	1.9417846000
*D90086	Pyruvate dehydrogenase beta subunit	-2.3701197000
L41143	Expressed pseudo TCTA at t(1;3) translocation site	-2.3607117000
M63573	Secreted cyclophilin-like protein (SCYLP)	1.9226736000
*X64072	CD18; Also: M15395	1.9213222000
Z22548	Thiol-specific antioxidant protein	-2.3496417000
M72885	GOS2; Also: M69199_rna1	1.9171115000
HG1067-HT1067	Mucin/M22406	1.9114934000
M80397	DNA polymerase delta catalytic subunit; Also: M81735	-2.3239221000
M22632	Mitochondrial aspartate aminotransferase	-2.3186893000
*X00734	Beta-tubulin (5-beta) with ten Alu family members	-2.2901738000
J04501	Muscle glycogen synthase	1.8619822000
L13266	N-methyl-d-aspartate receptor (NR1-1)	-2.2750809000
D16583	L-histidine decarboxylase	1.8302678000
X87212	Cathepsin C	1.8308174000
U76366	Treacher Collins syndrome (TCOF1); Also: U84665, U40847	-2.2445863000
X69433	Mitochondrial isocitrate dehydrogenase (NADP+)	-2.2474823000
Z29331	(23k/3) ubiquitin-conjugating enzyme UbcH2	1.8159097000

D63487	KIAA0153	-2.2291697000
U73799	Dynactin/U73799	1.7998573000
D12625	Neurofibromin	1.7918309000
D82348	Aminoimidazole carboxamide ribo-nt transmylase/inosinicase	-2.2076344000
M36542	Lymphoid-specific transcription factor; Also: X13810, X13809	-2.2043574000
M21665	Beta-myosin heavy chain; Also: X52889	1.7723363000
U89336	Notch 4	-2.1940632000
J04132	T cell receptor zeta-chain	1.7635777000
U79271	Clones 23920 and 23921 sequence	1.7502416000
AC000099	Cosmid g0771a003	-2.1675758000
D90276	CGM7 nonspecific cross-reacting antigen (NCA)	-2.1670957000
HG3995-HT4265	Cpg-Enriched Dna Clone S19	-2.1596800000
AF002224	E6-AP ubiquitin protein ligase 3A/promoter P1	1.7346798000
X67325	p27	-2.1546522000
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L32137	Germline oligomeric matrix protein (COMP)	1.7239480000
Z46632	HSPDE4C1 3 ,5 -cyclic AMP phosphodiesterase	1.7264012000
Y08409	Spot14	-2.1407044000
U56976	Calmodulin dependent phosphodiesterase PDE1B1	1.7128601000
X04145	T-cell receptor T3 gamma polypeptide	1.7165042000
M13755	Interferon-induced 17-kDa/15-kDa protein	-2.1362051000
S66431	RBP2=retinoblastoma binding protein 2	1.7037212000
M98045	Folylpolyglutamate synthetase	-2.1298107000
U47621	Nucleolar autoantigen No55	1.6981708000
X57351	1-8D from interferon-inducible family	-2.1186367000
HG491-HT491	Fc Receptor Iib3 For Igg, Low Affinity	1.6904619000
X89986	NBK apoptotic inducer protein; Also: U49730, U34584	1.6868596000
HG3987-HT4257	Cpg-Enriched Dna Clone E06	-2.1094182000
AD000684	LISCH7 (liver-specific bHLH-Zip transcription factor)	1.6814222000
**X05299	(~95%) major centromere autoantigen CENP-B	1.6791289000
AF001294	IPL	-2.1022192000
U50743	NaK-ATPase gamma subunit	-2.0976043000
M65085	Follicle stimulating hormone receptor	1.6673862000
M35252	CO-029	-2.0848443000
L36463	Ras inhibitor (Rin1)	1.6544690000
U79261	Clone 23959; Also: U62317_rna1	-2.0810321000
X99142	Hair keratin hHb6	-2.0812573000
HG3991-HT4261	Cpg-Enriched Dna, Clone E18	1.6428106000
U13369	Ribosomal DNA repeating unit/U13369	1.6399345000
U46746	Dystrobrevin-epsilon; Also: U46744	1.6422686000
M13207	Granulocyte-macrophage colony-stimulating factor (CSF1)	-2.0635210000
X69838	G9a	-2.0635210000
Z22555	Encoding CLA-1	-2.0576186000
Z33905	43kD acetylcholine receptor-associated protein (Rapsyn)	1.6197193000
U39573	Salivary peroxidase	-2.0552349000
J03600	Lipoxygenase	-2.0488301000
Y00757	Polypeptide 7B2	-2.0487933000
L13698	Growth-arrest-specific protein (gas)	1.6115584000
U22662	Nuclear orphan receptor LXR-alpha	1.6076694000
X17360	HOX 5.1 protein	1.6118826000
Z38133	Myosin; Also: M36769	1.6092717000

X70991	MADER	1.6063349000
M13981	Inhibin A-subunit	1.6011419000
U49260	Mevalonate pyrophosphate decarboxylase (MPD)	-2.0366788000
AF009674	Axin	1.5857071000
U91316	Acyl-CoA thioester hydrolase	-2.0287237000
D86971	KIAA0217	1.5813868000
HG2797-HT2906	Clathrin, Light Polypeptide B- Also: X81637, HG2797-HT2905	-2.0267375000
M16707	Histone H4; clone FO108.	-2.0251522000
D50923	KIAA0133	1.5725231000
S69369	PAX3A=TRANSCRIPTION FACTOR	1.5694910000
M63582	Preprothyrotropin-releasing hormone	-2.0136797000
D49493	Bone morphogenetic protein-3b	1.5591882000
AC002115	COX6B	-2.0121515000
X98833	Zinc finger protein, Hsal1	-2.0089194000
D50532	Macrophage lectin 2	1.5516018000
D50913	KIAA0123	-2.0061450000
M25322	Granule membrane protein-140	-2.0059844000
M33882	p78 protein	-2.0057702000
X06956	HALPHA44 alpha-tubulin	-2.0045900000
M64231	Spermidine synthase	-1.9982048000
HG3748-HT4018	Basic Transcription Factor 44 Kda Subunit	1.5370001000
K03021	Tissue plasminogen activator (PLAT)	-1.9892829000
Z14244	CoxVIIb cytochrome c oxidase subunit VIIb	-1.9903944000
U37219	cyclophilin-like protein CyP-60	-1.9864918000
D50402	NRAMP1	1.5099211000
HG2259-HT2348	Tubulin, Alpha 1; Also: X06956	-1.9746844000
HG2463-HT2559	Guanine Nucleotide-Binding protein G25k	-1.9741085000
X04201	Skeletal muscle tropomyosin	-1.9737627000
X97630	Serine threonine protein kinase EMK	-1.9752020000
J00220	IGHA1 from Ig germline H-chain G-E-A region A: gamma-3 5	1.4976974000
L76568	S26 from excision and cross link repair protein ERCC4/L76568	-1.9693577000
M96944	B-cell specific TRANSCRIPTION FACTOR (BSAP)	1.4969988000
U01828	Microtubule-associated protein 2 (MAP2)	1.4951973000
U96629	Hereditary multiple exostosis	1.4901693000
M60298	Erythrocyte membrane protein band 42 (EPB42)	1.4847268000
*U89606	Pyridoxal kinase	1.4845845000
U22970	16-Jun (interferon-inducible peptide precursor)	-1.9576671000
U01157	Glucagon-like peptide-1 receptor with CA dinucleotide repeat	1.4775752000
X16282	Zinc finger protein (clone 647)	1.4782778000
X81851	IL-4 splice variant/X81851; Also: M13982	1.4752438000
U25988	Pregnancy-specific glycoprotein 13 (PSG1)	-1.9489628000
X71490	Vacuolar proton ATPase subunit D	-1.9519443000
X05908	Lipocortin	1.4691078000
D86956	KIAA0201	1.4661771000
X13589	Aromatase (estrogen synthetase)	1.4643405000
Z14093	Branched chain decarboxylase alpha subunit	1.4654723000
*M85220	Heavy chain disease IgA chain CH3 region	1.4526297000
U02031	Sterol regulatory element binding protein-2	1.4533794000
L21993	Adenylyl cyclase	1.4503590000
D84454	UDP-galactose translocator	1.4436628000
U20240	C/EBP gamma	1.4431197000

D84557	HsMcm6	-1.9302484000
M62843	Antigen of paraneoplastic sensory neuronopathy patients	-1.9305033000
U65676	Hermansky-Pudlak syndrome protein (HPS)	1.4405943000
Z22780	Cylicin	1.4387218000
X89101	Fas (Apo-1, CD95)/X89101; Also: X83493, X63717, X83492	-1.9231144000
L25444	TAFII70-alpha	-1.9207102000
X52008	Strychnine binding subunit of inhibitory glycine receptor	-1.9199275000
*M58459	Ribosomal protein (RPS4Y) isom	-1.9165197000
U78525	Eukaryotic translation initiation factor (eIF3)	-1.9140786000
X52611	Transcription factor AP-2; Also: HG2465-HT4871, M36711	-1.9158613000
U60415	bHLH-PAS protein Jap3	1.4213571000
AF000545	Putative purinergic receptor P2Y10	-1.9043097000
*M35999	Platelet glycoprotein IIIa (GPIIIa)	1.4089180000
X07743	Pleckstrin (P47)	1.4044376000
X56687	Autoantigen NOR-90; Also: X53461, X53390, U65487_rna1	-1.8983823000
M87507	Interleukin-1 beta convertase (IL1BCE); Also: U13697	1.4005185000
U83598	Death domain receptor 3 soluble form (DDR3); Also: U94512	-1.8947313000
*X07109	Protein kinase C (PKC) type beta II	-1.8952153000
M76446	Alpha-A1-adrenergic receptor	1.3928727000
D38498	PMS5 (yeast PMS1 homolog)	-1.8904909000
U64998	Ribonuclease k6 precursor/U64998	1.3909219000
U91327	Chromosome 12p15 BAC clone CIT987SK-99D8 sequence	1.3911998000
U18235	ATP-binding cassette protein (ABC2) HFBCD04 clone	1.3866834000
U18919	Chromosome 17q12-21 clone pOV-2	1.3860456000
L19183	MAC30	-1.8868431000
D43968	AML1b protein	-1.8803133000
M94065	Dihydroorotate dehydrogenase	-1.8800272000
U38268	Cytochrome b pseudo/U38268	-1.8799556000
U61262	Neogenin	-1.8810992000
U87964	Putative G-protein (GP-1)	-1.8814560000
L48692	(clone p5-23-3)	1.3767594000
HG167-HT167	Hypothetical protein Npiiy20/M76676	1.3646448000
J04449	(clone NF 10) cytochrome P-450 nifedipine oxidase	1.3637999000
D83784	KIAA0198	-1.8699647000
X16667	HOX2G from the Hox2 locus	-1.8693784000
HG2755-HT2862	T-Plastin	-1.8637688000
U96094	Sarcolipin (SLN)	-1.8651040000
X01038	Fetal apolipoprotein AI precursor; Also: X07496, X00566	-1.8629658000
X77794	Cyclin G1	-1.8655481000
HG2992-HT5186	Beta-Hexosaminidase Alpha Polypeptide	1.3552284000
L09708	Complement component 2 (C2) allele b	1.3547290000
M24486	Prolyl 4-hydroxylase alpha subunit; Also: M24487, U14620_1	1.3536952000
U27699	PephBGT-1 betaine-GABA transporter	1.3549090000
Z34974	Plakophilin; Also: X79293	1.3510229000
D82061	Short-chain alcohol dehydrogenase family	-1.8595886000
D84361	p52 and p64 N-Shc	-1.8598285000
U64197	Chemokine exodus	-1.8589881000
M58460	75-kD autoantigen (PM-Sc1)	1.3408405000
U28749	High-mobility group phosphoprotein isoform I-C (HMGIC)	1.3392448000
U49973	Tigger 1 transposable element	1.3372595000
*D84145	WS-3	-1.8500333000

HG982-HT982	Pre-T/Nk-Cell-Associated protein 1f6; Also: L17326	-1.8476498000
X62078	GM2 activator protein	-1.8455631000
M19684	Alpha-1-antitrypsin-related protein	1.3239736000
U51003	DLX-2 (Dlx2); Also: L07919	1.3250466000
M15169	Beta-2-adrenergic receptor	1.3215725000
M22403	Blood platelet membrane glycoprotein Ib-alpha (GPIB)	1.3166020000
U43916	Tumor-associated membrane protein homolog (TMP)	1.3161801000
D16581	8-oxo-dGTPase	-1.8333200000
U00946	Clone A9A2BRB5 (CAC)n/(GTG)n repeat-containing	1.3119428000
*U62317	Hypothetical protein 384D8_7	1.3095598000
HG2707-HT2803	Serine/Threonine Kinase	1.3074800000
L75847	Zinc finger protein 45 (ZNF45)	1.3063484000
AF001548	815A9.1 myosin heavy chain from chromosome 16 BAC	-1.8301883000
M59916	Acid sphingomyelinase (ASM)	-1.8284988000
S75578	4-aminobutyrate aminotransferase/S75578; Also: L32961	-1.8297861000
M83822	Beige-like protein (BGL)	1.3001886000
M96132	MHC class II HLA-DR-beta-1*09012 (HLA-DRB1*09012)	1.3008128000
J02943	Corticosteroid binding globulin	-1.8248577000
M60299	Alpha-1 collagen type II s 1 2 and 3/M60299	-1.8246952000
HG3088-HT3263	Splicing Factor Sc35 m 3	1.2950756000
X78925	HZF2 zinc finger protein	1.2900346000
M73481	Gastrin releasing peptide receptor (GRPR)	-1.8188030000
L11931	Cytosolic serine hydroxymethyltransferase (SHMT)	1.2870175000
X60487	H4/h H4 histone	1.2873538000
U38964	PMS2 related (hPMSR2); Also: D38502	-1.8154117000
M17183	Parathyroid hormone-related protein; Also: M24351_3, J03580	1.2785250000
D85433	MURR1	-1.8097280000
Z48481	Membrane type matrix metalloproteinase 1	-1.8082110000
M87860	S-lac lectin L-14-II (LGALS2)	1.2683541000
L32866	Effector cell protease receptor-1 (EPR-1)	-1.8044802000
M11726	Pancreatic polypeptide	-1.8053309000
Z84721	DNA from 16p13.3 Contains alpha and zeta globin	-1.8031156000
S58733	pp52=B lymphocyte signal transduction	1.2642308000
D14446	HFREP-1	-1.7990820000
D37931	RNase 4	-1.8018323000
*M11749	Thy-1 glycoprotein	-1.7987879000
U01120	Glucose-6-phosphatase	-1.7976137000
HG3570-HT3773	Protein Phosphatase Inhibitor Homolog	-1.7935634000
Z72499	Herpesvirus associated ubiquitin-specific protease (HAUSP)	-1.7969211000
U28488	Putative G protein-coupled receptor (AZ3B); Also: U62027	1.2483725000
U20860	Angiotensin II type 2 receptor	1.2451424000
L00205	K6b epidermal keratin type II	-1.7875490000
S74683	ADP-ribosyltransferase	-1.7919537000
U63336	MHC Class I region proline rich protein	-1.7902852000
HG896-HT896	Thrombospondin 2	1.2414220000
M27878	DNA binding protein (HPF2)	1.2395497000
U39226	Myosin VIIA (USH1B)	1.2376463000
X79510	Protein-tyrosine-phosphatase D1	1.2361010000
L08424	Achaete scute homologous protein (ASH1)	-1.7847064000
HG2614-HT2710	Collagen Type Viii Alpha 1	1.2321764000
Z70218	MN1 protein (clone ICRFp507I0498); Also: X82209	1.2278215000

U59228	Ectodermal dysplasia protein (EDA)	-1.7784226000
U44848	Nuclear respiratory factor 1 (NRF1)/U44848/	1.2209368000
HG3242-HT3419	Calcium Channel, Voltage-Gated, Alpha 1e Subunit, 2	-1.7753767000
M25809	Endomembrane proton pump subunit	-1.7725967000
M27318	Interferon (IFN-alpha-M1)	1.2139137000
X51757	Heat-shock protein HSP70B'	1.2104790000
X99350	HFH4	1.2102298000
Y08564	GalNAc-T4/Y08564	1.2076344000
HG4258-HT4528	Kinase Inhibitor P27kip1 Cyclin-Dependent	-1.7678976000
HG919-HT919	Dna Polymerase Epsilon Catalytic Subunit	-1.7714956000
D83920	Uterus ficolin-1	1.2042557000
M62505	C5a anaphylatoxin receptor	1.2027830000
Y08766	Splicing factor, SF1-Bo isoform; Also: L49380	1.2049504000
M32334	Intercellular adhesion molecule 2 (ICAM-2)	-1.7634280000
S79781	WT1/S79781	-1.7641855000
X54380	Pregnancy zone protein	1.1975562000

TABLE 5. Gene targets in MS spinal cord white matter from a sample with minimal to no inflammation.

Probe set	Gene description	log10 (ratio) fold change
M84739	Autoantigen calreticulin	2.9768541000
M13755	Interferon-induced 17-kDa/15-kDa protein	-2.6319001000
M29194	Triglyceride lipase	2.7169627000
M77829	Channel-like integral membrane protein (CHIP28); Also: S73482	2.6933453000
AF001359	Mismatch repair protein (hMLH1)/AF001359	-2.4844422000
X95876	G-protein coupled receptor	-2.4699324000
AB000896	Cadherin FIB2	-2.4188397000
L48513	Paraoxonase 2 (PON2)	-2.4034637000
M21904	4F2 glycosylated heavy chain (4F2HC) antigen	2.5422028000
D49818	Fructose 6-phosphate 2-kinase/fructose 2 6-bisphosphatase	2.5278232000
X00734	Beta-tubulin (5-beta) with ten Alu family members	2.5225746000
***D16480	Mitochondrial enoylCoA hydratase	2.4726833000
M96326	Azurocidin	-2.3481101000
U35234	Protein tyrosine phosphatase sigma	2.4405943000
M65066	cAMP-dependent protein kinase regulatory subunit RI-beta	-2.3362095000
X86401	L-arginine:glycine amidinotransferase	2.4148938000
AB000895	Cadherin FIB1	-2.3181155000
D87433	KIAA0246	-2.3191061000
U45328	Ubiquitin-conjugating enzyme (UBE2I); Also: U31882, U66867	2.3617749000
D50863	TESK1	-2.2965007000
*D61391	Phosphoribosypyrophosphate synthetase-associated protein 39	-2.2951821000
HG3945-HT4215	Phospholipid Transfer protein	2.3041673000
AD000092	RAD23A homolog	-2.2698630000
M60299	Alpha-1 collagen type II s 1 2 and 3/M60299	2.2705624000
U37219	Cyclophilin-like protein CyP-60	-2.2589364000
M90299	Glucokinase (GCK)	-2.2545481000
L24774	Delta3, delta2-CoA-isomerase; Also: Z25821_rna1, Z25820	2.2454882000
D43968	AML1b protein	-2.2463139000
M63573	Secreted cyclophilin-like protein (SCYLP)	2.2362475000

U12707	Wiskott-Aldrich syndrome protein (WASP); Also: U19927	2.2370408000
D63486	KIAA0152	2.2290416000
D15049	Protein tyrosine phosphatase	-2.2322971000
M96684	Pur (pur-alpha)	2.2042557000
J02947	Extracellular-superoxide dismutase (SOD3)	2.1949304000
L05148	Protein tyrosine kinase related sequence	-2.2048658000
M36429	Transducin beta-2 subunit; Also: M16538	2.1834122000
U66559	Anaplastic lymphoma kinase receptor	-2.1918002000
X17651	Myf-4 myogenic determination factor	-2.1869563000
K03189	Chorionic gonadotropin beta subunit	2.1595672000
L41067	NF-AT4c	-2.1758016000
J04501	Muscle glycogen synthase	2.1481347000
S78085	PDCD2=programmed cell death-2/Rp8 homolog	-2.1691599000
X81372	Biphenyl hydrolase-related protein	-2.1664301000
U03270	Centrin	-2.1609185000
U24183	Phosphofructokinase (PFKM); Also: HG1849-HT1878	2.1302939000
J00268	Insulin; Also: V00565, X70508, L15440, M10039	-2.1558672000
D28423	Pre-splicing factor SRp20	2.1225435000
L76702	B56-delta	2.1264561000
M91585	Br140	2.1259690000
M57609	DNA-binding protein (GLI3)	-2.1494501000
X15331	Phosphoribosylpyrophosphate synthetase subunit one	2.1215598000
L00205	K6b epidermal keratin type II	-2.1467480000
L43579	(clone 110298)/L43579; Also: L43575	2.1151110000
D49490	Disulfide isomerase-related protein	-2.1380657000
M31776	M25296 and others	2.1119343000
U23430	Cholecystokinin type A receptor (CCK-A); Also: L19315	2.1105897000
X04366	Calcium activated neutral protease large subunit (muCANP)	-2.1371166000
D80003	KIAA0181	-2.1313780000
D14822	CBFA2T1	-2.1245042000
U82671	HSP1-A from cosmids from Xq28	2.0900816000
U40002	Hormone-sensitive lipase testicular isoform; Also: L11706	2.0870323000
Z48314	Apomucin; Also: U06711	2.0870712000
HG3242-HT4231	Calcium Channel, Voltage-Gated, Alpha 1e Subunit, 3	-2.1080574000
D30755	KIAA0113	-2.1044871000
U77968	Neuronal PAS1 (NPAS1)	2.0672569000
J02645	Translational initiation factor (eIF-2) alpha subunit	-2.0896402000
U49278	Putative DNA-binding protein	-2.0898168000
L32866	Effector cell protease receptor-1 (EPR-1)	-2.0857364000
X13810	OTF-2 lymphoid-specific transcription factor; Also: M36542	-2.0805363000
U15131	p126 (ST5)	2.0398106000
D11094	MSS1	2.0364293000
AB000409	MNK1	-2.0695756000
S81737	Alpha 1 syntrophin; Also: U40571	2.0324173000
M58026	NB-1	2.0184925000
X13956	12S RNA induced by poly(rI) poly(rC) and Newcastle virus	-2.0547088000
D28532	Renal Na+-dependent phosphate cotransporter	-2.0486360000
X99142	Hair keratin hHb6	2.0111474000
U15655	Ets domain prot ERF	2.0045363000
U16031	TRANSCRIPTION FACTOR IL-4 Stat	-2.0447357000

U78793	Folate receptor alpha (hFR)/U78793	-2.0437551000
HG4757-HT5207	Oncogene Mll-Af4, Fusion Activated; Also: L13773	-2.0424771000
L38503	Glutathione S-transferase theta 2 (GSTT2)	-2.0343276000
D13988	Rab GDI	1.9896722000
M96738	Somatostatin receptor subtype 3 (SSTR3); Also: Z86000	1.9881128000
U86759	Netrin-2 like protein (NTN2l); Also: U86758_rna1	1.9829493000
D84239	IgG Fc binding protein	-2.0197392000
AF002224	E6-AP ubiquitin protein ligase 3A/promoter P1	1.9738203000
*M94250	Retinoic acid inducible factor (MK)	1.9708116000
X68688	ZNF33B; Also: D31763	-2.0095571000
M91083	DNA-binding protein (HRC1)	1.9637878000
L41143	Expressed pseudo TCTA at t(1;3) translocation site	1.9602033000
U08191	R kappa B; Also: X80878	1.9614211000
X54637	Tyk2 non-receptor protein tyrosine kinase	1.9566486000
D79998	KIAA0176	-1.9967305000
U71364	Serine protase inhibitor (P19)	-1.9973864000
M32879	Steroid 11-beta-hydroxylase (CYP11B1)	1.9385197000
*U37408	CtBP	1.9400182000
X02958	Interferon alpha IFN-alpha 6	-1.9815921000
M15881	Uromodulin (Tamm-Horsfall glycoprotein)	-1.9748570000
U85658	TRANSCRIPTION FACTOR ERF-1	-1.9673139000
X12517	U1 small nuclear RNP-specific C protein	1.9188164000
U78180	Sodium channel 2 (hBNaC2)	-1.9604708000
M21984	(clone PWHTnT16) skeletal muscle Troponin T	-1.9555675000
X16260	Inter-alpha-trypsin inhibitor subunit 3; Also: X69532_rna1	1.9103576000
X63380	RSRFR2	1.9033593000
M21389	Keratin type II (58 kD)	-1.9454686000
U07919	Aldehyde dehydrogenase 6	-1.9452223000
X76942	U41740 and others	-1.9463294000
X89101	Fas (Apo-1, CD95)/X89101; Also: X83493, X63717, X83492	-1.9459607000
J05582	Pancreatic mucin; Also: J05581	1.9006585000
M22919	Non-muscle myosin light chain MLC	-1.9378939000
L08488	Inositol polyphosphate 1-phosphatase	1.8954482000
U68723	Checkpoint suppressor 1	1.8934843000
X82850	Thyroid transcript factor 1; Also: U43203, U33749	1.8945929000
M59916	Acid sphingomyelinase (ASM)	1.8904865000
X07315	PP15 (placental protein 15)	1.8901415000
X58298	Interleukin-6-receptor; Also: M20566	1.8918161000
U37519	Aldehyde dehydrogenase (ALDH8)	-1.9301847000
HG3884-HT4154	Homeotic protein Hpx-42	1.8873359000
**X05299	(~95%) major centromere autoantigen CENP-B	1.8790959000
X13293	B-myb	1.8782345000
D79985	KIAA0163	-1.9194703000
J00220	IGHA1 from Ig germline H-chain G-E-A region A: gamma-3 5	1.8759989000
J03171	Interferon-alpha receptor (HuIFN-alpha-Rec)	-1.9122221000
U44754	PSE-binding factor PTF gamma subunit	-1.9075457000
U53442	p38Beta MAP kinase	-1.9100905000
*X64072	CD18; Also: M15395	1.8668778000
M15465	Pyruvate kinase type L; Also: D13243	-1.9063350000
X87870	Hepatocyte nuclear factor 4a	-1.9037680000
L43338	(clone JJ1a) cadherin/L43338	-1.8995469000

Z19002	PLZF kruppel-like zinc finger protein	-1.8955607000
U89896	Casein kinase I gamma 2	1.8524800000
D45917	TIMP-3; Also: U14394	-1.8909796000
U06698	Neuronal kinesin heavy chain	-1.8904210000
L02867	62 kDa paraneoplastic antigen	1.8457180000
M21302	Small proline rich protein (sprII), clone 174N	1.8464883000
U60116	Skeletal muscle LIM-protein SLIM2	1.8438554000
X81420	hHKb1 protein	1.8452505000
AB002315	KIAA0317	-1.8874766000
D86971	KIAA0217	1.8337844000
L31881	Nuclear factor I-X	1.8360075000
X59303	G7a valyl-tRNA synthetase; Also: M98326	1.8369567000
U65011	Preferentially expressed antigen of melanoma (PRAME)	-1.8787920000
Z71389	Skin-antimicrobial-peptide 1 (SAP1)/Z71389	-1.8800987000
U15932	Dual-specificity protein phosphatase	-1.8727388000
X13766	Beta-casein; Also: L10615, X17070	-1.8754953000
X73079	Encoding Polymeric Ig receptor	-1.8757845000
U50360	Calcium, calmodulin-dependent protein kinase II gamma/U50360	1.8249558000
AF009674	Axin	-1.8701112000
M58297	Zinc finger protein 42 (MZF-1)	-1.8720105000
U65093	Msg1-related 1 (mrg1)	-1.8704039000
U83192	Post-synaptic density protein 95 (PSD95)	1.8185558000
J05614	Proliferating cell nuclear antigen (PCNA) promoter region	1.8165727000
*M63438	Ig rearranged gamma chain , V-J-C region; Also: X96754	1.8081860000
U96769	Chondroadherin	1.8027737000
U83843	HIV-1 Nef interacting protein (Nip7-1)/U83843	1.7996851000
HG3495-HT3689	Collagen Type Ix Alpha 1	-1.8500333000
L47276	(cell line HL-60) alpha topoisomerase/L47276; Also: L47277	-1.8492658000
*M85220	Heavy chain disease IgA chain CH3 region	1.7895246000
U26266	Deoxyhypusine synthase/U26266; Also: U79262	1.7888751000
U09366	Zinc finger protein ZNF133	-1.8413595000
U17743	JNK activating kinase (JNKK1); Also: L36870	-1.8407332000
Y08374	GP-39 cartilage protein	-1.8399492000
U65404	Erythroid-specific TRANSCRIPTION FACTOR EKLF	1.7849737000
J02963	Platelet glycoprotein IIb	-1.8363241000
M84820	Retinoid X receptor beta (RXR-beta); Also: X63522, X65463	-1.8347385000
Z35309	Adenylyl cyclase	-1.8325089000
D87457	KIAA0281	1.7785130000
X74328	CB2 (peripheral) cannabinoid receptor	1.7792356000
X79483	ERK6 extracellular signal regulated kinase	1.7785130000
Z16411	Phospholipase c; Also: U26425, Z37544_rna1	1.7817554000
Z80345	SCAD; Also: M26393	1.7813963000
D49817	Fructose 6-phosphate 2-kinase/fructose 2 6-bisphosphatase	1.7767012000
X97444	Transmembrane protein Tmp21-IIex/X97444	1.7726884000
Y07566	RIT protein	-1.8238002000
M36089	DNA-repair protein (XRCC1)	1.7723217000
X86018	MUF1 protein	1.7671559000
Y12478	CHD5 protein	1.7635395000
Z69881	Adenosine triphosphatase calcium	-1.8223316000
X60655	EVX1	1.7558749000
D14686	Glycine cleavage system T-protein	-1.8098962000

U01160	Transmembrane 4 superfamily protein (SAS)	-1.8108715000
HG162-HT3165	Tyrosine Kinase Receptor Axl 2	1.7516639000
K02054	Gastrin-releasing peptide	-1.8056707000
L00137	Growth hormone releasing factor	-1.8029447000
V00565	Preproinsulin; Also: M10039	1.7431176000
U08989	Glutamate transporter	-1.8019180000
U79280	Clone 23575	-1.8014895000
M38258	Retinoic acid receptor gamma 1	1.7359979000
X69115	ZNF37A zinc finger protein	-1.7964009000
HG3033-HT3194	Spliceosomal protein Sap 62	1.7284743000
M23294	Beta-hexosaminidase beta-subunit (HEXB)	1.7275413000
X14830	Muscle acetylcholine receptor beta-subunit	-1.7894044000
X98507	Myosin-I beta	-1.7876376000
D87078	KIAA0235	1.7267272000
U08049	Peripheral myelin protein-22 (PMP22) non-coding 1A/U08049	-1.7837250000
U14910	RPE-retinal G protein-coupled receptor (rgr)	-1.7830098000
U90547	Ro/SSA ribonucleoprotein homolog (RoRet)	-1.7831887000
D28383	ATP synthase B chain	1.7185017000
U70732	Glutamate pyruvate transaminase (GPT)	1.7178323000
D10495	Protein kinase C delta-type	1.7168377000
L78833	Ifp35 from BRCA1, Rho7 and vatl	1.7155856000
M37457	Na+,K+ -ATPase catalytic subunit alpha-III isoform	1.7147488000
U77846	Elastin	-1.7806773000
U87972	NAD+-isocitrate dehydrogenase/U87972	-1.7804973000
U35113	Metastasis-associated mta1	1.7084209000
X07876	Irp prot (int-1 related protein)	-1.7772455000
X90858	Uridine phosphorylase	-1.7732377000
Y08682	Carnitine palmitoyltransferase I type I; Also: U62733, U62317	-1.7767012000
U20428	SNC19 sequence	1.7071442000
L41919	HIC-1 fragment	-1.7691926000
M11186	Prepro-oxytocin-neurophysin I (OXT)	-1.7693773000
X62535	Diacylglycerol kinase	-1.7712199000
HG3523-HT4899	Proto-Oncogene C-Myc; Also: L00058, HG3523-HT4900	1.6980926000
X56687	Autoantigen NOR-90; Also: X53461, X53390, U65487_rna1	1.6998235000
J04449	(clone NF 10) cytochrome P-450 nifedipine oxidase	-1.7654823000
L40386	DP-2; Also: U18422	1.6946052000
L37199	(clone cD24-1) Huntington's disease candidate regiont	1.6879746000
U52373	Serine/threonine kinase MNB (mnb); Also: D85759, D86550	1.6916708000
L18920	MAGE-2	-1.7604225000
*M87789	Hybridoma H210 anti-hepatitis A IgG V, C, CDR regions	1.6826464000
U40490	Nicotinamide nucleotide transhydrogenase	1.6852938000
L43964	(clone F-T03796) STM-2	-1.7531999000
X96753	Chondroitin sulfate proteoglycan (MCSP)	-1.7562556000
D42053	KIAA0091	1.6794279000
HG3437-HT3628	Myelin Proteolipid protein; Also: M54927	1.6731273000
M21665	Beta-myosin heavy chain; Also: X52889	1.6762362000
M31169	Propionyl-CoA carboxylase beta-subunit/M31169	1.6720979000
AF005361	Importin alpha 6	-1.7435098000
M91196	DNA-binding protein	-1.7448795000
U35139	NECDIN related protein	1.6669857000
M22324	Aminopeptidase N	-1.7395723000

*M74826	Glutamate decarboxylase (GAD-2)	-1.7407573000
X60957	Tie putative receptor tyrosine kinase	-1.7393745000
HG4518-HT4921	Transcription Factor Btf3 Homolog M90355	1.6603911000

TABLE 6. Gene targets in MS spinal cord white matter from a sample with lymphocytic inflammation, demyelination and axonal loss.

Probe set	Gene description	log10 (ratio) fold change
*M63438	Ig rearranged gamma chain , V-J-C region; Also: X96754	2.8860030000
AB000584	TGF-beta superfamily protein	-2.9452516000
L00389	Cytochrome P-450 4	-2.9300826000
M84739	Autoantigen calreticulin	2.6676864000
M13755	Interferon-induced 17-kDa/15-kDa protein	-2.6319001000
HG3945-HT4215	Phospholipid Transfer protein	2.4979657000
*M87789	Anti-hepatitis A IgG V, C, CDR regions; Also: J00221_2	2.4941391000
D26561	ORF E7 from papillomavirus 5b genome	-2.4064124000
HG3033-HT3194	Spliceosomal protein Sap 62	2.4704774000
U22970	16-Jun (interferon-inducible peptide precursor)	-2.3853381000
X93996	AFX protein	2.4455264000
M21904	4F2 glycosylated heavy chain (4F2HC) antigen	2.4151404000
AB000895	Cadherin FIB1	-2.3181155000
Y00757	Polypeptide 7B2	-2.3219607000
M96684	Pur (pur-alpha)	2.3033041000
D17716	N-acetylglucosaminyltransferase V	-2.2915353000
M16653	Pancreatic elastase IIB	-2.2924222000
HG3995-HT4265	Cpg-Enriched Dna Clone S19	-2.2683997000
D10495	Protein kinase C delta-type	2.2642273000
D63486	KIAA0152	2.2668195000
J04501	Muscle glycogen synthase	2.2589870000
U37219	Cyclophilin-like protein CyP-60	-2.2589364000
D43968	AML1b protein	-2.2463139000
X67325	p27	-2.2399248000
U12707	Wiskott-Aldrich syndrome protein (WASP); Also: U19927	2.2246625000
*X64072	CD18; Also: M15395	2.2272438000
M33882	p78 protein	-2.2166936000
U45328	Ubiquitin-conjugating enzyme (UBE2I); Also: U31882	2.1997661000
U40279	Beta-2 integrin alphaD subunit (ITGAD)/U40279	-2.1967977000
X53683	LAG-1	-2.1972116000
*X13334	CD14 myeloid cell-specific leucine-rich glycoprotein	2.1776808000
L41143	Expressed pseudo TCTA at t(1;3) translocation site	2.1658892000
U87964	Putative G-protein (GP-1)	-2.1662080000
M63573	Secreted cyclophilin-like protein (SCYLP)	2.1523334000
HG3987-HT4257	Cpg-Enriched Dna Clone E06	-2.1621161000
L00205	K6b epidermal keratin type II	-2.1467480000
X95406	Cyclin E	-2.1339379000
M77829	Channel-like integral membrane protein (CHIP28)	2.1191604000
M61199	Cleavage signal 1 protein	2.1075491000
U82310	Unknown protein/U82310	-2.1044871000
M28825	Thymocyte antigen CD1a	-2.0982975000
U15655	Ets domain protein ERF	2.0989896000
M23294	Beta-hexosaminidase beta-subunit (HEXB)	2.0948204000
L32866	Effector cell protease receptor-1 (EPR-1)	-2.0857364000

K03189	Chorionic gonadotropin beta subunit	2.0920185000
L76702	B56-delta	2.0888446000
X13810	OTF-2 lymphoid-specific transcription factor; Also: M36542	-2.0805363000
J02947	Extracellular-superoxide dismutase (SOD3)	2.0849336000
D50402	NRAMP1	2.0795430000
X54637	Tyk2 non-receptor protein tyrosine kinase	2.0818871000
AB000409	MNK1	-2.0695756000
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HG162-HT3165	Tyrosine Kinase Receptor Axl 2	2.0771862000
HG4243-HT4513	Zinc Finger protein Znf155	-2.0479560000
**X05299	(~95%) major centromere autoantigen CENP-B	2.0411952000
HG2614-HT2710	Collagen Type Viii Alpha 1	2.0360297000
U02619	TFIIIC Box B-binding subunit	2.0366289000
D87937	Alpha(1,2)fucosyltransferase 5	-2.0150452000
M98045	Folylpolyglutamate synthetase	-2.0156740000
*M94250	Retinoic acid inducible factor (MK)	2.0295867000
M63967	Mitochondrial aldehyde dehydrogenase x	-2.0057166000
Y11306	Beta catenin/TCF-4	2.0193240000
*U60269	Putative ERVK envelope protein	-2.0017337000
X59766	Zn-alpha2-glycoprotein	-1.9977139000
M38258	Retinoic acid receptor gamma 1	2.0157788000
D79998	KIAA0176	-1.9967305000
U71364	Serine protase inhibitor (P19)	-1.9973864000
L02867	62 kDa paraneoplastic antigen	2.0036759000
L10386	Transglutaminase E3 (TGASE3)	1.9989129000
M36429	Transducin beta-2 subunit; Also: M16538	1.9967305000
U80669	Androgen regulated homeobox protein (NKX31)	-1.9772662000
HG3928-HT4198	SFTPA2D	1.9860996000
J04948	Alkaline phosphatase (ALP-1)	1.9865478000
U17969	Initiation factor eIF-5A	-1.9667282000
M20681	Glucose transporter-like protein-III (GLUT3)	-1.9596375000
M24594	Interferon-inducible 56 Kd protein	-1.9576073000
M86826	IGF binding protein complex acid-labile subunit a	1.9715078000
M21984	(clone PWHTnT16) skeletal muscle Troponin T	-1.9555675000
M35252	CO-029	-1.9542425000
*U37408	CtBP	1.9580858000
U32576	Apolipoprotein apoC-IV (APOC4)	-1.9517017000
M21389	Keratin type II (58 kD)	-1.9454686000
U07919	Aldehyde dehydrogenase 6	-1.9452223000
L24774	Delta3, delta2-CoA-isomerase; Also: Z25821_rna1, Z25820	1.9465301000
U37519	Aldehyde dehydrogenase (ALDH8)	-1.9301847000
U12139	Alpha1(XI) collagen (COL11A1)/U12139	1.9232440000
U33920	Clone lambda 5 semaphorin	1.9253121000
S75989	Gamma-aminobutyric acid transporter type 3	-1.9180303000
V00565	Preproinsulin; Also: M10039	1.9114240000
U53442	p38Beta MAP kinase	-1.9100905000
M15465	Pyruvate kinase type L; Also: D13243	-1.9063350000
K02100	Ornithine transcarbamylase (OTC)	-1.8898617000
X00734	Beta-tubulin (5-beta) with ten Alu family members	1.8830934000
AB002315	KIAA0317	-1.8874766000
X04470	Antileukoprotease (ALP) from cervix uterus; Also: X04503	1.8810992000

U15932	Dual-specificity protein phosphatase	-1.8727388000
X13766	Beta-casein; Also: L10615, X17070	-1.8754953000
M58297	Zinc finger protein 42 (MZF-1)	-1.8720105000
D42053	KIAA0091	1.8588379000
S74445	Cellular retinoic acid-binding protein	1.8589298000
U15131	p126 (ST5)	1.8576340000
U28368	Id-related helix-loop-helix protein Id4	1.8527849000
AF006609	RGS3	1.8510028000
D49357	S-adenosylmethionine synthetase	1.8491122000
U12595	Tumor necrosis factor type 1 receptor associated protein TRAP1	-1.8570308000
U35234	Protein tyrosine phosphatase sigma	1.8379039000
S78432	Un-named-transcript-1 from SAS=transmembrane 4 protein	-1.8457180000
L31881	Nuclear factor I-X	1.8350561000
U93049	SLP-76 associated protein	1.8372727000
U17743	JNK activating kinase (JNKK1); Also: L36870	-1.8407332000
Z26256	L-type calcium channel/Z26256	1.8286599000
D25539	KIAA0040	-1.8345796000
L07738	DHP-sensitive calcium channel gamma subunit (CACNLG)	1.8224950000
X06956	HALPHA44 alpha-tubulin	1.8215490000
Y10207	CD171 protein/Y10207	1.8202015000
X52056	Spi-1 proto-oncogene	1.8075350000
S81294	DCC=deleted in colorectal cancer/S81294	-1.8149132000
U28488	Putative G protein-coupled receptor (AZ3B); Also: U62027	1.8041394000
U22029	Cytochrome P450 (CYP2A7)	-1.8080421000
X92896	ITBA2 protein	-1.8077041000
L00137	Growth hormone releasing factor	-1.8029447000
X07315	PP15 (placental protein 15)	1.7856857000
L13720	Growth-arrest-specific protein (gas)	1.7777892000
J04469	Mitochondrial creatine kinase (CKMT)	-1.7906370000
U85767	Myeloid progenitor inhibitory factor-1 MPIF-1	-1.7895807000
X14830	Muscle acetylcholine receptor beta-subunit	-1.7894044000
M74093	Cyclin	-1.7830098000
L40407	Thyroid receptor interactor (TRIP9)	1.7708520000
X53002	Integrin beta-5 subunit; Also: J05633	1.7701153000
U87972	NAD+-isocitrate dehydrogenase/U87972	-1.7804973000
M32053	H19 RNA (spliced in silico)	1.7634280000
U27333	Alpha (1,3) fucosyltransferase (FUT6) , major transcript I	1.7652959000
L40393	(clone S171)	1.7570162000
J04449	(clone NF 10) cytochrome P-450 nifedipine oxidase	-1.7654823000
U03494	Transcription factor LSF	-1.7667845000
U82306	Unknown protein/U82306	1.7493498000
X17094	Furin	1.7497363000
M96980	Myelin TRANSCRIPTION FACTOR 1 (MTF1)	1.7425180000
M20642	Alkali myosin light chain 1; Also: X05451, M20643	-1.7607993000
S76942	Dopamine D4 receptor; Also: L12398, HG944-HT944	-1.7606109000
U18018	E1A enhancer binding protein (E1A-F)	-1.7604464000
M81933	Cdc25A	1.7403627000
HG620-HT620	Tyrosine Phosphatase Epsilon	-1.7531999000
Y10506	CD110 protein/Y10506	-1.7547305000
U78524	Gu binding protein	1.7351995000
M29540	Carcinoembryonic antigen (CEA)	-1.7522406000

U35113	Metastasis-associated mta1	1.7283538000
D50913	KIAA0123	-1.7435098000
M22324	Aminopeptidase N	-1.7395723000
X55740	Placental cDNA coding nucleotidase (EC 3135)	-1.7383841000
S81737	Alpha 1 syntrophin; Also: U40571	1.7185017000
U03399	T-complex protein 10A (TCP10A)	1.7197455000
M24351	PTH-like hormone A	-1.7327287000
Y09858	Unknown protein	1.7134905000
U20428	SNC19 sequence	1.7109631000
D13633	KIAA0008	-1.7281508000
U55764	Estrogen sulfotransferase	-1.7281508000
D49817	Fructose 6-phosphate 2-kinase/fructose 2 6-bisphosphatase	1.7067178000
U15197	Histo-blood group ABO protein	1.7058637000
X89109	Coronin; Also: D44497	1.7056006000
HG896-HT896	Thrombospondin 2	-1.7248900000
S70585	Thyroid-stimulating hormone alpha subunit	-1.7226339000
U25433	Protein associated with tumorigenic conversion (CATR13)	-1.7252989000
U82979	Ig-like transcript-3	-1.7236609000
D28383	ATP synthase B chain	1.6985355000
D29956	KIAA0055	1.6994041000
M57732	Hepatic nuclear factor 1 (TCF1)	-1.7201593000
U60521	Protease proMch6 (Mch6)	-1.7220166000
X52008	Strychnine binding subunit of inhibitory glycine receptor	-1.7182940000
AF015950	Telomerase reverse transcriptase	1.6932872000
D78156	RasGTPase activating protein	1.6946052000
M73077	Glucocorticoid receptor repression factor 1 (GRF-1)	-1.7077830000
U58681	Neurogenic basic-helix-loop-helix protein (NeuroD2)	-1.7113854000
HG273-HT273	Lymphocyte Antigen Hla-G3; Also: J03027	1.6830470000
S77361	Transcript ch132/S77361	1.6826793000
M81780	SMPD1	-1.7041505000
U41804	Putative T1/ST2 receptor binding protein precursor	-1.7056499000
X04706	Homeobox (clone HHO.c13); Also: X17360_rna1	-1.7052221000
U89896	Casein kinase I gamma 2	1.6789734000
HG4318-HT4588	Lim-Domain Transcription Factor Lim-1; Also: U14755	-1.6987528000
U08021	Nicotinamide N-methyltransferase (NNMT)	-1.7019995000
X52228	Secreted epithelial tumour mucin antigen	-1.7002709000
X73079	Encoding Polymeric Ig receptor	-1.6996932000
X15331	Phosphoribosylpyrophosphate synthetase subunit one	1.6734817000
S58733	pp52=B lymphocyte signal transduction	-1.6941663000
D87077	KIAA0240	1.6707096000
U46461	Dishevelled homolog (DVL)	1.6688516000
X86018	MUF1 protein	1.6720979000
M81882	Glutamate decarboxylase (GAD65)	-1.6917444000
Z38133	Myosin; Also: M36769	-1.6899744000
U83192	Post-synaptic density protein 95 (PSD95)	1.6637009000
L43579	(clone 110298)/L43579; Also: L43575	1.6584884000
U21049	DD96	1.6618127000
L24203	Ataxia-telangiectasia group D-associated protein	-1.6855178000
U49248	Canalicular multispecific organic anion transporter (cMOAT)	-1.6839471000
M28219	Low density lipoprotein receptor	1.6532125000
M64929	Protein phosphatase 2A alpha subunit	1.6536948000

U08096	Peripheral myelin protein-22 (PMP22) non-coding 1B/U08096	1.6565773000
M27749	Ig-related 14.1 protein	-1.6814674000
S38742	HOX11=HOX11 homeodomain {homeobox}; Also: M75952	-1.6780629000
U45983	G protein-coupled receptor GPR-CY6	-1.6801088000
X95240	Cysteine-rich secretory protein-3; Also: X94323	-1.6780629000
J02854	20-kDa myosin light chain (MLC-2)	-1.6748611000
D38081	Thromboxane A2 receptor	1.6459133000
D82346	HNSPC	1.6449307000
D88799	Cadherin	1.6468936000
M59820	Granulocyte colony-stimulating factor receptor (CSF3R)	1.6444386000
U33838	NF-kappa-B p65delta3 , spliced transcript	-1.6690843000
AF002224	E6-AP ubiquitin protein ligase 3A/promoter P1	1.6389882000
X16260	Inter-alpha-trypsin inhibitor subunit 3; Also: X69532_rna1	1.6379898000
D21063	KIAA0030	-1.6641717000
Z19574	Cytokeratin 17	-1.6662839000
U68723	Checkpoint suppressor 1	1.6359861000
D90064	CGM6 CD66b (NCA-95)	-1.6611025000
U05012	Receptor tyrosine kinase TrkC (NTRK3); Also: S76475	-1.6618127000
M14219	Chondroitin/dermatan sulfate proteoglycan (PG40) core protein	1.6324573000
X97444	Transmembrane protein Tmp21-IIex/X97444	1.6294096000
Z11502	Intestine-specific annexin	1.6304279000
M84526	Adipsin/complement factor D	1.6235563000
U81523	Endometrial bleeding associated factor	1.6268534000
X87212	Cathepsin C	1.6242821000
D29640	KIAA0051; Also: L33075	-1.6490914000
U32674	Orphan receptor GPR9 (GPR9); Also: X95876	-1.6466487000
X65873	Kinesin (heavy chain)	1.6154240000
X70218	Protein phosphatase X	1.6133132000
M59371	Protein tyrosine kinase	-1.6414741000
U43916	Tumor-associated membrane protein homolog (TMP)	-1.6337209000
U33429	K+ channel beta 2 subunit	1.6047659000
X16706	Fra-2	1.6036815000
X90780	Cardiac troponin I	1.6063814000
X76498	Uterine bombesin receptor	-1.6276219000
HG3893-HT4163	Phosphoglucomutase 1	1.6009729000
S83308	SOX5=Sry-related HMG box	1.6009729000
U64197	Chemokine exodus	1.5982432000
K02777	T-cell receptor active alpha-chain from Jurkat cell line	-1.6260836000
U07794	Tyrosine kinase (TXK)	-1.6227320000
X98337	Complement factor H-related protein 4; Also: X68679	-1.6271097000
D29992	Placental protein 5 (PP5)	1.5932861000
X51698	Spasmolytic polypeptide (SP); Also: U47292	1.5971465000
AF005887	ATF family member ATF6	-1.6211763000
HG3432-HT3618	Fibroblast Growth Factor Receptor K-Sam	-1.6198756000
HG537-HT537	Collagen Type Viii Alpha 2	-1.6188323000
M60278	Heparin-binding EGF-like growth factor	-1.6216955000
M83738	Protein-tyrosine phosphatase (PTPase MEG2)	-1.6175245000
X99975	hRTR/hGCNF protein	-1.6188323000
U40223	Uridine nucleotide receptor (UNR)	1.5888317000
M84820	Retinoid X receptor beta (RXR-beta); Also: X63522, X65463	-1.6172546000
U04313	Maspin	-1.6143698000

U16997	Orphan receptor ROR gamma	-1.6173935000

TABLE 7. Gene targets in MS spinal cord white matter from a sample with inflammation by macrophages and demyelination.

Probe set	Gene description	log10 (ratio) fold chang
*M63438	Ig rearranged gamma chain , V-J-C region	3.0608377000
HG1614-HT1614	Protein Phosphatase 1 Alpha Catalytic Subunit	-2.6832272000
L76200	Guanylate kinase (GUK1)	-2.6705781000
U02619	TFIIIC Box B-binding subunit	2.7524326000
M91083	DNA-binding protein (HRC1)	2.7402837000
U35234	Protein tyrosine phosphatase sigma	2.7303381000
M95787	22kDa smooth muscle protein (SM22)	-2.6407546000
M13755	Interferon-induced 17-kDa/15-kDa protein	-2.6319001000
U72507	40871 sequence	-2.5803547000
*M87789	Anti-hepatitis A IgG V, C, CDR regions	2.5829467000
L41143	Pseudo TCTA at t(1;3) translocation site	2.5372864000
S68616	Na+/H+ exchanger NHE-1 isom	-2.5223464000
X00734	Beta-tubulin (5-beta) with ten Alu family members	2.4960990000
J04948	Alkaline phosphatase (ALP-1)	2.4679779000
AB002318	KIAA0320	-2.4959950000
M27826	Endogenous retroviral protease	-2.4913967000
X79882	Irp	-2.4741434000
S73885	AP-4=basic helix-loop-helix DNA-binding protein	-2.4527445000
U12707	Wiskott-Aldrich syndrome protein (WASP)	2.4106085000
X12517	U1 small nuclear RNP-specific C protein	2.4070508000
D84361	p52 and p64 N-Shc	-2.4451759000
M21388	Unproductively rearranged Ig mu-chain V-region VD	-2.4238600000
D87452	KIAA0263	-2.4207394000
U12139	Alpha1(XI) collagen (COL11A1)/U12139	2.3716219000
U45328	Ubiquitin-conjugating enzyme (UBE2I)	2.3701682000
*U37408	CtBP	2.3659557000
D26561	ORF E7 from papillomavirus 5b genome	-2.4064124000
U40490	Nicotinamide nucleotide transhydrogenase	2.3468418000
M60299	Alpha-1 collagen type II s 1 2 and 3/M60299	2.3402458000
U22970	16-Jun (interferon-inducible peptide precursor)	-2.3853381000
AF002224	E6-AP ubiquitin protein ligase 3A/promoter P1	2.3358589000
L77213	Phosphomevalonate kinase	-2.3777159000
U40223	Uridine nucleotide receptor (UNR)	2.3265407000
HG162-HT3165	Tyrosine Kinase Receptor Axl 2	2.3128118000
J02947	Extracellular-superoxide dismutase (SOD3)	2.3059959000
AF015910	Unknown protein	-2.3407910000
L08246	Myeloid cell differentiation protein (MCL1)	-2.3375591000
D87433	KIAA0246	-2.3191061000
U86759	Netrin-2 like protein (NTN2l); Also: U86758_rna1	2.2712606000
X07315	PP15 (placental prot 15)	2.2678754000
D86977	KIAA0224	-2.3159179000
M22632	Mitochondrial aspartate aminotransferase	-2.3137091000
X71135	Sox3	2.2587570000
AB000895	Cadherin FIB1	-2.3095154000

Z26256	L-type calcium channel/Z26256	2.2564772000
D42053	KIAA0091	2.2499318000
*D61391	Phosphoribosypyrophosphate synthetase-associated protein 39	-2.2951821000
M58286	TNF receptor; Also: M63121, M33294, X55313, M75866	-2.2938596000
U02566	Receptor tyrosine kinase tif; Also: U18934	-2.2947417000
U60116	Skeletal muscle LIM-prot SLIM2	2.2412974000
X89416	Protein phosphatase 5	2.2405866000
D90084	Pyruvate dehydrogenase alpha subunit	-2.2917018000
M16653	Pancreatic elastase IIB	-2.2924222000
D25303	Integrin alpha subunit	-2.2749656000
X81420	hHKb1 protein	2.2188077000
AD000092	RAD23A homolog	-2.2698630000
L19711	Dystroglycan (DAG1)	-2.2611439000
D31833	Vasopressin V1b receptor; Also: L37112	2.2053397000
J05582	Pancreatic mucin; Also: J05581	2.2060018000
L24774	Delta3, delta2-CoA-isomerase; Also: Z25821_rna1, Z25820	2.2038512000
M84739	Autoantigen calreticulin	2.2049335000
U37219	Cyclophilin-like protein CyP-60	-2.2546151000
L38517	Indian hedgehog protein (IHH)	2.1964718000
U51010	Nicotinamide N-methyltransferase 1 and 5 ing region	2.1883659000
M24400	Chymotrypsinogen	2.1859669000
U05861	Hepatic dihydrodiol dehydrogenase	-2.2392995000
X67325	p27	-2.2399248000
U23803	Heterogeneous ribonucleoprotein A0	2.1817007000
X54637	Tyk2 non-receptor protein tyrosine kinase	2.1769590000
D15049	Protein tyrosine phosphatase	-2.2322971000
*X64072	CD18; Also: M15395	2.1707017000
AF000545	Putative purinergic receptor P2Y10	-2.2244036000
D50855	Ca-sensing receptor; Also: U20760, U20759	-2.2251800000
U37221	Cyclophilin-like protein	2.1582117000
L02321	Glutathione S-transferase (GSTM5)	-2.2208922000
K03189	Chorionic gonadotropin beta subunit	2.1563977000
M34344	Platelet glycoprotein IIb (GPIIb)	-2.2134513000
X04201	Skeletal muscle tropomyosin	-2.2087772000
*M85220	Heavy chain disease IgA chain CH3 region	2.1465908000
X59842	PBX2; Also: U89336_2, D28769_1, X80700_rna1	2.1397217000
Z49254	L23-related	-2.2020794000
M21665	Beta-myosin heavy chain; Also: X52889	2.1256439000
M94167	Heregulin-beta2	2.1230345000
X52896	Dermal fibroblast elastin; Also: HG2994-HT4851	2.1256439000
D38305	Tob	-2.1898507000
U66559	Anaplastic lymphoma kinase receptor	-2.1918002000
D13635	KIAA0010	2.1218880000
M34376	Beta-microseminoprotein (MSP); Also: X57928	2.1207384000
X14767	GABA-A receptor, beta 1 subunit	-2.1846914000
X17651	Myf-4 myogenic determination factor	-2.1869563000
L38929	Protein tyrosine phosphatase delta	2.1154441000
M25809	Endomembrane proton pump subunit	2.1134085000
HG3570-HT3773	Protein Phosphatase Inhibitor Homolog	-2.1780412000
M92287	Cyclin D3 (CCND3)	-2.1800542000

M77698	GLI-Krupple related protein (YY1)	-2.1748590000
D43767	Chemokine	-2.1684238000
*U52518	Grb2-related adaptor protein (Grap)	2.0925452000
U27333	Alpha (1,3) fucosyltransferase (FUT6) , major transcript I	2.0845763000
J05252	Also: M95971	2.0731683000
U23430	Cholecystokinin type A receptor (CCK-A); Also: L19315	2.0766404000
HG3934-HT4204	G1 Phase-Specific	-2.1499116000
X99142	Hair keratin hHb6	2.0715138000
L00205	K6b epidermal keratin type II	-2.1467480000
M35128	Muscarinic acetylcholine receptor	-2.1447706000
S85963	hIRS-1=rat insulin receptor substrate-1 homolog	2.0629578000
X63359	UGT2BIO udp glucuronosyltransferase	2.0668847000
HG4518-HT4921	Transcription Factor Btf3 Homolog M90355	2.0608866000
M25269	Tyrosine kinase (ELK1) onco	2.0620176000
HG2755-HT2862	T-Plastin	-2.1371958000
L25878	p33/HEH epoxide hydrolase (EPHX)	-2.1326599000
X95406	Cyclin E	-2.1339379000
D80003	KIAA0181	-2.1313780000
M80563	CAPL protein	-2.1310570000
*U28811	Cysteine-rich fibroblast growth factor receptor (CFR-1)	-2.1317790000
HG4068-HT4338	Phosphoprotein Tal2	2.0472749000
S80335	Integrin beta 7 subunit	2.0451273000
D14822	CBFA2T1	-2.1245042000
J02783	Thyroid hormone binding protein (p55)	-2.1270238000
M36089	DNA-repair protein (XRCC1)	2.0374878000
U42412	AMP-activated protein kinase gamma-1 subunit	-2.1207384000
X12433	pHS1-2 with ORF homolog to membrane receptor proteins	-2.1131910000
D88799	Cadherin	2.0236639000
X15331	Phosphoribosylpyrophosphate synthetase subunit one	2.0203613000
U65011	Preferentially expressed antigen of melanoma (PRAME)	-2.1092410000
D30755	KIAA0113	-2.1044871000
D50930	KIAA0140	-2.1026052000
U20428	SNC19 sequence	2.0117818000
U83192	Post-synaptic density protein 95 (PSD95)	2.0096633000
HG2825-HT2949	Ret Transforming	-2.0982045000
M28825	Thymocyte antigen CD1a	-2.0982975000
AC002086	PAC clone DJ525N14/Xq23	2.0030295000
L02867	62 kDa paraneoplastic antigen	2.0034605000
***D16480	Mitochondrial enoylCoA hydratase	1.9986952000
U65404	Erythroid-specific TRANSCRIPTION FACTOR EKLF	2.0002171000
L10386	Transglutaminase E3 (TGASE3)	1.9951963000
L05500	Fetal brain adenylyl cyclase	1.9921115000
U15655	Ets domain prot ERF	1.9914476000
M16405	m4 muscarinic acetylcholine receptor	-2.0841292000
X86570	Acidic hair keratin 1	-2.0854690000
D82345	NB thymosin beta	1.9813655000
U15131	p126 (ST5)	1.9820450000
U17838	Zinc finger protein RIZ	-2.0785474000
M75106	Prepro-plasma carboxypeptidase B	1.9738203000
D12625	Neurofibromin	1.9633155000
U83843	HIV-1 Nef interacting prot (Nip7-1)/U83843	1.9644953000

U96769	Chondroadherin	1.9654369000
Z48512	XG (clone PEP6)/Z48512	-2.0719740000
D87078	KIAA0235	1.9580858000
M36429	Transducin beta-2 subunit; Also: M16538	1.9609462000
M58026	NB-1	1.9609462000
U33920	Clone lambda 5 semaphorin	1.9607086000
D83920	Uterus ficolin-1	1.9572406000
X80910	PPP1CB	-2.0673499000
AB000897	Cadherin FIB3	-2.0600365000
M86933	Amelogenin (AMELY); Also: M55419, U79549_rna1, M55418	-2.0580462000
X79066	ERF-1	-2.0611559000
X60486	H4/g H4 histone	-2.0529824000
D28532	Renal Na+-dependent phosphate cotransporter	-2.0486360000
L41668	UDP Galactose 4 epimerase	-2.0491211000
U16031	TRANSCRIPTION FACTOR IL-4 Stat	-2.0447357000
U84540	Dystrobrevin isom DTN-3 (DTN)/U84540	-2.0471775000
X01715	Acetylcholine receptor gamma subunit precursor	-2.0451273000
HG3033-HT3194	Spliceosomal protein Sap 62	1.9207327000
L41066	NF-AT3	1.9175055000
U57057	WD protein IR10	1.9214263000
AF001294	IPL	-2.0404143000
M60614	Wilms tumor (WIT-1) associated protein	-2.0378248000
HG2417-HT2513	Dynein Heavy Chain	1.9066044000
M61199	Cleavage signal 1 protein	1.9057959000
J04611	Lupus p70 (Ku) autoantigen protein	-2.0357298000
L38503	Glutathione S-transferase theta 2 (GSTT2)	-2.0343276000
X17098	PSG10 pregnancy specific glycoprotein 10	1.9014583000
X74328	CB2 (peripheral) cannabinoid receptor	1.8987252000
D82060	Kidney histidine rich putative membrane protein	-2.0292823000
J04056	Carbonyl reductase	-2.0295867000
M23263	Androgen receptor	-2.0285713000
HG3945-HT4215	Phospholipid Transfer protein	1.8887410000
M23294	Beta-hexosaminidase beta-subunit (HEXB)	1.8878985000
M96684	Pur (pur-alpha)	1.8895818000
L17327	Pre-T/NK cell associated protein (3B3)	-2.0245883000
M19888	Small proline rich protein (sprl), clone 128	-2.0258177000
S79873	H-lamp-2=lysosome-associated membrane protein-2	-2.0271457000
X57351	1-8D from interferon-inducible family	-2.0254083000
X74819	Cardiac troponin T	1.8825245000
M55621	N-acetylglucosaminyltransferase I (GlcNAc-TI)	1.8793826000
Z36714	Cyclin F	1.8788089000
D84239	IgG Fc binding protein	-2.0175732000
S72370	Pyruvate carboxylase	-2.0198430000
U24576	Breast tumor autoantigen sequence	-2.0212927000
HG172-HT3924	Spermidine/Spermine N1-Acetyltransferase	1.8767950000
X63755	High-sulphur keratin	1.8709888000
D87937	Alpha(1,2)fucosyltransferase 5	-2.0150452000
M62324	Modulator recognition factor I (MRF-1)	-2.0143105000
U22377	Zn-15 related zinc finger protein (rlf)	1.8588379000
D28588	KIAA0048	-2.0045363000
M63967	Mitochondrial aldehyde dehydrogenase x	-2.0057166000

X02176	Complement component C9; Also: K02766	1.8488047000
D86983	KIAA0230	1.8450337000
D49818	Fructose 6-phosphate 2-kinase/fructose 2 6-bisphosphatase	1.8366405000
L29218	Clk2	1.8374843000
U09002	NMDA receptor modulatory subunit 2A (hNR2A)	1.8334659000
HG4683-HT5108	Tumor Necrosis Factor Receptor 2 Associated protein Trap3	-1.9940971000
L13391	Helix-loop-helix basic phosphoprotein (G0S8)	-1.9964022000
M98447	Keratinocyte transglutaminase	-1.9956352000
U71364	Serine protase inhibitor (P19)	-1.9973864000
X63629	P cadherin	-1.9925535000
X80695	OXA1Hs	-1.9965117000
X98482	TNNT2 11/X98482	1.8299467000
X59618	RR2 small subunit ribonucleotide reductase	1.8267225000
X93996	AFX protein	1.8234742000
D29992	Placental protein 5 (PP5)	1.8175654000
J04970	Carboxypeptidase M	1.8224950000
X04729	Plasminogen activator inhibitor type 1 N-terminus/X04729	1.8175654000
D31797	CD40 ligand	-1.9855387000
HG3578-HT3781	Autoimmune Antigen Thyroid Disease-Related Antigen	1.8123589000
*M13241	N-myc	1.8081145000
U05875	Interferon gamma receptor accessory factor-1 (AF-1)	1.8044061000
X04500	Prointerleukin 1 beta	1.8068580000
X92106	Bleomycin hydrolase	1.8020893000
U21049	DD96	1.7944880000
U91931	AP-3 complex beta3A subunit	1.7944880000
HG4593-HT4998	Sodium Channel 1	-1.9746268000
M15881	Uromodulin (Tamm-Horsfall glycoprotein)	-1.9748570000
D80004	KIAA0182	-1.9684829000
M13699	Ceruloplasmin (ferroxidase)	1.7788745000
D87449	KIAA0260	1.7770642000
M36803	Hemopexin	1.7759743000
S62028	Recoverin; Also: S43855	1.7756104000
X06182	C-kit proto-oncogene; Also: HG2549-HT3951	1.7745170000
M55682	Cartilage matrix protein (CMP); Also: M55683	1.7715875000
U17077	BENE	1.7678976000
HG3921-HT4191	Homeotic protein C6, Class I	-1.9577270000
M20681	Glucose transporter-like protein-III (GLUT3)	-1.9596375000
U78180	Sodium channel 2 (hBNaC2)	-1.9604708000
D88795	Cadherin	-1.9559282000
L34587	RNA polymerase II elongation factor SIII p15 subunit	-1.9548453000
M21984	(clone PWHTnT16) skeletal muscle Troponin T	-1.9555675000
U37248	Alpha-mannosidase (6A8)	-1.9553269000
U45285	Specific 116-kDa vacuolar proton pump subunit (OC-116KDa)	-1.9530345000
Z29083	5T4 Oncofetal antigen	-1.9550862000
X99140	Hair keratin hHb5	1.7489629000

TABLE 8. Gene targets in MS spinal cord white matter from a sample with inflammation by macrophages and lymphocytes and demyelination.

Probe set	Gene description	log10 (ratio) fold change
*M63438	Ig rearranged gamma chain , V-J-C region; Also: X96754	3.5479855000
L76200	Guanylate kinase (GUK1)	-2.6727442000
*M87789	Anti-hepatitis A IgG V, C, CDR regions; Also: J00221_2	2.9066259000
X74570	Gal-beta(1-3/1-4)GlcNAc alpha-23-sialyltransferase	-2.5341531000
HG3033-HT3194	Spliceosomal protein Sap 62	2.6505720000
HG3945-HT4215	Phospholipid Transfer protein	2.6058005000
D84361	p52 and p64 N-Shc	-2.4451759000
D50402	NRAMP1	2.4524994000
D26561	ORF E7 from papillomavirus 5b genome	-2.4064124000
U22970	16-Jun (interferon-inducible peptide precursor); Also: U22970	-2.3853381000
L27080	Melanocortin 5 receptor (MC5R)	2.3691787000
M84739	Autoantigen calreticulin	2.3240457000
D49817	Fructose 6-phosphate 2-kinase/fructose 2 6-bisphosphatase	2.3082442000
M96326	Azurocidin	-2.3481101000
HG3286-HT3463	Crystallin Alpha A	-2.3455208000
J03600	Lipoxygenase	-2.3282267000
L32976	Protein kinase (MLK-3)	-2.3323880000
M80397	DNA polymerase delta catalytic subunit; Also: M81735	-2.3273589000
J04948	Alkaline phosphatase (ALP-1)	2.2624986000
AB000895	Cadherin FIB1	-2.3181155000
Y00757	Polypeptide 7B2	-2.3219607000
X99142	Hair keratin hHb6	2.2411728000
*D61391	Phosphoribosypyrophosphate synthase-associated protein39	-2.2951821000
Y08409	Spot14	-2.2876898000
L14565	Peripherin (PRPH) s 1-9	2.2002210000
D13988	Rab GDI	2.1970461000
M23294	Beta-hexosaminidase beta-subunit (HEXB)	2.1922189000
U15131	p126 (ST5)	2.1918421000
HG2614-HT2710	Collagen Type Viii Alpha 1	2.1829707000
U37219	Cyclophilin-like protein CyP-60	-2.2589364000
U56816	Kinase Myt1 (Myt1)	-2.2537014000
U45328	Ubiquitin-conjugating enzyme (UBE2I); Also: U31882	2.1722622000
X67325	p27	-2.2399248000
*M94250	Retinoic acid inducible factor (MK)	2.1555486000
M55621	N-acetylglucosaminyltransferase I (GlcNAc-TI)	2.1510939000
J02947	Extracellular-superoxide dismutase (SOD3); Also: U10116	2.1296738000
U35234	Protein tyrosine phosphatase sigma	2.1262938000
X53683	LAG-1	-2.1972116000
X17651	Myf-4 myogenic determination factor	-2.1869563000
HG3570-HT3773	Protein Phosphatase Inhibitor Homolog	-2.1780412000
D10495	Protein kinase C delta-type	2.0939642000
M38258	Retinoic acid receptor gamma 1	2.0938243000

M27161	MHC class I CD8 alpha-chain (Leu-2/T8)	-2.1755118000
U13706	ELAV-like neuronal protein 1 isom Hel-N2 (Hel-N1)/U13706	-2.1692335000
X15331	Phosphoribosylpyrophosphate synthetase subunit one	2.0852549000
U87964	Putative G-protein (GP-1)	-2.1662080000
U77643	K12 protein precursor	2.0813599000
HG3987-HT4257	Cpg-Enriched Dna Clone E06	-2.1621161000
U12707	Wiskott-Aldrich syndrome protein (WASP); Also: U19927	2.0746519000
AB000462	SH3 binding RES4-23A	-2.1517587000
U12139	Alpha1(XI) collagen (COL11A1)/U12139	2.0644580000
X54637	Tyk2 non-receptor protein tyrosine kinase	2.0618105000
D49490	Disulfide isomerase-related protein	-2.1380657000
X95406	Cyclin E	-2.1339379000
M63582	Preprothyrotropin-releasing hormone	-2.1266184000
D14827	Tax helper protein 1	-2.1194209000
L29433	Factor X (blood coagulation factor)	2.0325785000
U93049	SLP-76 associated protein	2.0340667000
D83784	KIAA0198	-2.1156937000
D63486	KIAA0152	2.0280830000
L16991	Thymidylate kinase (CDC8)	2.0283882000
U15197	Histo-blood group ABO protein	2.0293026000
HG3242-HT4231	Calcium Channel, Voltage-Gated, Alpha 1e Subunit, 3	-2.1080574000
U65011	Preferentially expressed antigen of melanoma (PRAME)	-2.1092410000
U82310	Unknown protein/U82310	-2.1044871000
HG2290-HT2386	Calcitonin	-2.1007151000
M28825	Thymocyte antigen CD1a	-2.0982975000
X57110	HG642-HT642 and others	-2.0995943000
M31776	M25296 and others	2.0134061000
Y08263	AAD14 protein	-2.0928083000
U77968	Neuronal PAS1 (NPAS1)	2.0047512000
L38487	Estrogen receptor-related protein (hERRa1)	-2.0839503000
M16405	m4 muscarinic acetylcholine receptor	-2.0841292000
U96769	Chondroadherin	1.9994350000
U83192	Post-synaptic density protein 95 (PSD95)	1.9963584000
X79066	ERF-1	-2.0739931000
AB000409	MNK1	-2.0695756000
Z48512	XG (clone PEP6)/Z48512	-2.0719740000
X60486	H4/g H4 histone	-2.0529824000
L24774	Delta3, delta2-CoA-isomerase; Also: Z25821_rna1, Z25820	1.9747715000
U79273	Clone 23933 sequence	1.9728737000
X04898	Apolipoprotein AII	1.9733099000
X07315	PP15 (placental protein 15)	1.9728968000
L41668	UDP Galactose 4 epimerase	-2.0491211000
AF008445	Phospholipid scramblase	1.9705328000
AF001294	IPL	-2.0447357000
D13636	KIAA0011	-2.0416887000
L08488	Inositol polyphosphate 1-phosphatase	1.9596625000
Z48314	Apomucin; Also: U06711	1.9617769000
J04056	Carbonyl reductase	-2.0295867000
M21904	4F2 glycosylated heavy chain (4F2HC) antigen	1.9515075000
*X64072	CD18; Also: M15395	1.9479481000

U23430	Cholecystokinin type A receptor (CCK-A); Also: L19315	1.9457393000
M62324	Modulator recognition factor I (MRF-1)	-2.0143105000
D21851	KIAA0028	-2.0075344000
X64037	RNA polymerase II associated protein RAP74	-2.0115704000
U83303	GCP-2 (granulocyte chemotactic protein-2)	-2.0065730000
HG162-HT3165	Tyrosine Kinase Receptor Axl 2	1.9327020000
M81933	Cdc25A	1.9346247000
X04500	Prointerleukin 1 beta	1.9345489000
M61199	Cleavage signal 1 protein	1.9318391000
U28831	Protein immuno-reactive with anti-PTH polyclonal antibodies	1.9287542000
U35113	Metastasis-associated mta1	1.9319915000
X92106	Bleomycin hydrolase	1.9279859000
D79998	KIAA0176	-1.9967305000
HG4683-HT5108	Tumor Necrosis Factor Receptor 2 Associated protein Trap3	-1.9940971000
U71364	Serine protase inhibitor (P19)	-1.9973864000
U78524	Gu binding protein	1.9260336000
X17098	PSG10 pregnancy specific glycoprotein 10	1.9229848000
M15881	Uromodulin (Tamm-Horsfall glycoprotein)	-1.9748570000
D42053	KIAA0091	1.9100104000
M19311	Calmodulin	1.9089673000
HG3921-HT4191	Homeotic protein C6, Class I	-1.9577270000
U78180	Sodium channel 2 (hBNaC2)	-1.9604708000
L41143	Expressed pseudo TCTA at t(1;3) translocation site	1.8975177000
M21984	(clone PWHTnT16) skeletal muscle Troponin T	-1.9555675000
Z29083	5T4 Oncofetal antigen	-1.9550862000
L36463	Ras inhibitor (Rin1)	1.8962506000
U32576	Apolipoprotein apoC-IV (APOC4)	-1.9517017000
X13839	Vascular smooth muscle alpha-actin	-1.9479070000
L35240	Enigma	-1.9442358000
X07695	Cytokeratin 4	-1.9460836000
X89101	Fas (Apo-1, CD95)./X89101; Also: X83493, X63717, X83492	-1.9459607000
U15655	Ets domain protein ERF	1.8889934000
U02082	Guanine nucleotide regulatory protein (tim1)	-1.9407654000
U11690	Faciogenital dysplasia (FGD1)	1.8867726000
U65404	Erythroid-specific TRANSCRIPTION FACTORS EKLF	1.8825245000
U82818	UCP3S/U82818	1.8860826000
M96980	Myelin TRANSCRIPTION FACTORS 1 (MTF1)	1.8786190000
X93996	AFX protein	1.8819835000
D10511	Mitochondrial acetoacetyl-CoA thiolase	-1.9274987000
D79985	KIAA0163	-1.9194703000
M84424	Cathepsin E (CTSE)	-1.9196010000
M36089	DNA-repair protein (XRCC1)	1.8706560000
U02619	TFIIIC Box B-binding subunit	1.8707549000
U17566	65 kDa hydrophobic protein	1.8723894000
*L05624	MAP kinase kinase; Also: L11284	1.8667598000
U28488	Putative G protein-coupled receptor (AZ3B); Also: U62027	1.8656961000
J03171	Interferon-alpha receptor (HuIFN-alpha-Rec)	-1.9122221000
U53442	p38Beta MAP kinase	-1.9100905000
M15465	Pyruvate kinase type L; Also: D13243	-1.9063350000
X87870	Hepatocyte nuclear factor 4a	-1.9037680000
HG4390-HT4660	Ribosomal protein L18a Homolog	1.8601583000

*U37408	CtBP	1.8621016000
Z78289	(clone 1D2)/Z78289	1.8617404000
M11722	Terminal transferase	1.8534244000
HG831-HT831	Potassium Channel	-1.8930679000
J00220	IGHA1 from Ig germline H-chain G-E-A region A: gamma-3 5	1.8475357000
M59820	Granulocyte colony-stimulating factor receptor (CSF3R)	1.8484047000
K02100	Ornithine transcarbamylase (OTC)	-1.8898617000
L21998	Intestinal mucin (MUC2)	-1.8902813000
U06698	Neuronal kinesin heavy chain	-1.8904210000
U68233	Farnesol receptor HRR-1 (HRR-1)	-1.8884603000
M34516	Omega light chain protein 14.1 (Ig lambda chain related)	1.8469395000
M36429	Transducin beta-2 subunit; Also: M16538	1.8443529000
U29615	Chitotriosidase precursor	1.8448808000
U60116	Skeletal muscle LIM-protein SLIM2	1.8436687000
X60655	EVX1	1.8447256000
M74525	HHR6B (yeast RAD 6 homolog)	-1.8828090000
Z71389	Skin-antimicrobial-peptide 1 (SAP1)/Z71389	-1.8800987000
U15932	Dual-specificity protein phosphatase	-1.8727388000
X13766	Beta-casein; Also: L10615, X17070	-1.8754953000
D82346	HNSPC	1.8354052000
AF009674	Axin	-1.8701112000
U65093	Msg1-related 1 (mrg1)	-1.8704039000
U67733	Cyclic nucleotide phosphodiesterase PDE2A3	1.8279505000
*X13334	CD14 myeloid cell-specific leucine-rich glycoprotein	1.8282409000
AF000231	Rab11a GTPase	-1.8662873000
D83782	KIAA0199	-1.8634716000
Z29331	(23k/3) ubiquitin-conjugating enzyme UbcH2	1.8257506000
Y10262	EYA3/Y10262; Also: U81602	-1.8571817000
L47276	(cell line HL-60) alpha topoisomerase/L47276; Also: L47277	-1.8492658000
M57567	ADP-ribosylation factor (hARF5)	-1.8489585000
U51587	Golgi complex autoantigen golgin-97	-1.8501866000
U59058	Beta-A3/A1 crystallin (CYRBA3/A1); Also: M14306	-1.8490726000
HG909-HT909	Mg81	1.8123176000
U17743	JNK activating kinase (JNKK1); Also: L36870	-1.8407332000
J05582	Pancreatic mucin; Also: J05581	1.8041208000
Z35309	Adenylyl cyclase	-1.8325089000
L13720	Growth-arrest-specific protein (gas)	1.8010262000
U83843	HIV-1 Nef interacting protein (Nip7-1)/U83843	1.7976829000
X70683	SOX-4 protein	1.7998573000
M60746	Histone H3.1 (H1F3)	-1.8265607000
U27333	Alpha (1,3) fucosyltransferase (FUT6) , major transcript I	1.7928468000
U33920	Clone lambda 5 semaphorin	1.7951150000
Z69881	Adenosine triphosphatase calcium	-1.8223316000
U08096	Peripheral myelin protein-22 (PMP22) 1B/U08096	1.7898979000
U48861	Beta 4 nicotinic acetylcholine receptor subunit	1.7900387000
S81294	DCC=deleted in colorectal cancer/S81294	-1.8149132000
L01406	Growth hormone-releasing hormone receptor	1.7840464000
M91585	Br140	1.7844746000
D11094	MSS1	1.7794161000
L31881	Nuclear factor I-X	1.7732377000
M24486	Prolyl 4-hydroxylase alpha subunit; Also: M24487, U14620_1	1.7737864000

HG4115-HT4385	Olfactory Receptor Or17-210	-1.7984780000
L38929	Protein tyrosine phosphatase delta	1.7706311000
U43843	H-neuro-d4 prot	-1.7955324000
M13981	Inhibin A-subunit	1.7638022000
M25269	Tyrosine kinase (ELK1)	1.7632033000
U67611	Mouse transaldolase/U67611	1.7644277000
Z26256	L-type calcium channel/Z26256	1.7674898000
X14830	Muscle acetylcholine receptor beta-subunit	-1.7894044000
L22548	Collagen type XVIII alpha 1 (COL18A1)	1.7594412000
X53296	IRAP; Also: X64532_rna1, X52015	1.7616648000
X81420	hHKb1 prot	1.7594729000
D49818	Fructose 6-phosphate 2-kinase/fructose 2 6-bisphosphatase	1.7560272000
HG3884-HT4154	Homeotic protein Hpx-42	1.7532382000
M64929	Protein phosphatase 2A alpha subunit	1.7537745000
U06088	N-acetylgalactosamine 6-sulphatase (GALNS)	-1.7779703000
U77846	Elastin	-1.7806773000
U87972	NAD+-isocitrate dehydrogenase/U87972	-1.7804973000
D49357	S-adenosylmethionine synthetase	1.7486144000
X86401	L-arginine:glycine amidinotransferase; Also: S68805	1.7521582000
X07876	Irp protein (int-1 related protein)	-1.7772455000
X52011	MYF6 encoding a muscle determination factor	-1.7734207000
*M24766	Alpha-2 collagen type IV (COL4A2); Also: X05610	1.7465174000
M58026	NB-1	1.7429214000
U22377	Zn-15 related zinc finger protein (rlf)	1.7474118000
U28368	Id-related helix-loop-helix protein Id4	1.7455432000
X13293	B-myb	1.7445668000
X53002	Integrin beta-5 subunit; Also: J05633	1.7436665000
L41919	HIC-1 fragment	-1.7691926000
M11186	Prepro-oxytocin-neurophysin I (OXT)	-1.7693773000
M96684	Pur (pur-alpha)	1.7398096000
X65873	Kinesin (heavy chain)	1.7411122000
J04449	(clone NF 10) cytochrome P-450 nifedipine oxidase	-1.7654823000
U28131	HMGI-C chimeric transcript	-1.7626786000
X87160	Epithelial amiloride-sensitive sodium channel gamma	1.7337989000
M20642	Alkali myosin light chain 1; Also: X05451, M20643	-1.7607993000
U59111	Dermatan sulfate proteoglycan 3 (DSPG3)	-1.7585334000
M77829	Channel-like integral membrane protein (CHIP28)	1.7323536000
X16260	Inter-alpha-trypsin inhibitor subunit 3; Also: X69532_rna1	1.7297721000
X68090	Fc-gamma-RIIA IgG Fc receptor class IIA/X68090	1.7286378000
X68836	S-adenosylmethionine synthetase	1.7323133000
HG620-HT620	Tyrosine Phosphatase Epsilon	-1.7531999000
L43964	(clone F-T03796) STM-2	-1.7531999000
X96753	Chondroitin sulfate proteoglycan (MCSP)	-1.7562556000
Y10506	CD110 protein/Y10506	-1.7547305000
M91083	DNA-binding protein (HRC1)	1.7237839000
L34155	Laminin-related protein (LamA3)	-1.7485756000
X66362	PCTAIRE-3 serine/threonine protein kinase	-1.7478001000
AF005361	Importin alpha 6	-1.7435098000
D50913	KIAA0123	-1.7435098000
M91196	DNA-binding protein (HRC1)	-1.7448795000
X17094	Furin	1.7140782000

X56199	XIST a (locus DXS399E)	1.7144136000
X90872	gp25L2 protein	1.7174239000
M22324	Aminopeptidase N	-1.7395723000
*M74826	Glutamate decarboxylase (GAD-2)	-1.7407573000
U71203	Rit; Also: Y07566	-1.7377888000
X63359	UGT2BIO udp glucuronosyltransferase	1.7031624000
X97444	Transmembrane protein Tmp21-liex./X97444	1.7065898000

TABLE 9. Gene targets in MS spinal cord white matter from a sample with axonal loss.

Pr b set	Gene descripti n	log10 (ratio) fold change
*M63438	Ig rearranged gamma chain , V-J-C region; Also: X96754	3.9579713000
AB000584	TGF-beta superfamily protein	-2.9495730000
*M87789	Anti-hepatitis A IgG V, C, CDR regions; J00221	3.3816210000
L76200	Guanylate kinase (GUK1)	-2.6727442000
M27504	Topoisomerase type II (Topo II)/M27504/Also: Z15115	3.0841507000
M84739	Autoantigen calreticulin	2.9484496000
U45878	Inhibitor of apoptosis protein 1; Also: L49432	-2.5991459000
U22398	Cdk-inhibitor p57KIP2 (KIP2)	-2.5926486000
HG3033-HT3194	Spliceosomal protein Sap 62	2.7255114000
J04794	Aldehyde reductase	-2.5857708000
M24486	Prolyl 4-hydroxylase alpha subunit; Also: M24487, U14620_1	2.4710569000
X74570	Gal-beta(1-3/1-4)GlcNAc alpha-23-sialyltransferase	-2.5341531000
D64142	Histone H1x	-2.5299434000
M21904	4F2 glycosylated heavy chain (4F2HC) antigen	2.4384632000
S68616	Na+/H+ exchanger NHE-1 isom	-2.5223464000
AB002318	KIAA0320	-2.4959950000
M27826	Endogenous retroviral protease	-2.4913967000
HG2614-HT2710	Collagen Type Viii Alpha 1	2.3734545000
U12707	Wiskott-Aldrich syndrome protein (WASP); Also: U19927	2.3664510000
*U37408	CtBP	2.3356885000
X86691	218kD Mi-2 protein	-2.4076458000
U02619	TFIIIC Box B-binding subunit	2.2834708000
X99142	Hair keratin hHb6	2.2847916000
D26561	ORF E7 from papillomavirus 5b genome	-2.4064124000
U35234	Protein tyrosine phosphatase sigma	2.2769785000
D11086	Interleukin 2 receptor gamma	-2.3887671000
U22970	16-Jun (interferon-inducible peptide precursor); U22970	-2.3853381000
D31833	Vasopressin V1b receptor; Also: L37112	2.2463878000
S76475	TrkC from brain	-2.3536759000
D63486	KIAA0152	2.2292978000
M96326	Azurocidin	-2.3481101000
M91083	DNA-binding protein (HRC1)	2.2142609000
U23803	Heterologous ribonucleoprotein A0	2.2093005000
X54637	Tyk2 non-receptor protein tyrosine kinase	2.2109202000
J03600	Lipoxygenase	-2.3282267000
Z11502	Intestine-specific annexin	2.1989181000
AB000895	Cadherin FIB1	-2.3181155000
M12125	Fibroblast muscle-type tropomyosin	-2.3107464000
D49817	Fructose 6-phosphate 2-kinase/fructose 2 6-bisphosphatase	2.1814434000
D42085	KIAA0095	-2.3021685000
D49818	Fructose 6-phosphate 2-kinase/fructose 2 6-bisphosphatase	2.1724424000
M79463	PML-2; Also: HG560-HT560, M82827	-2.2904798000
U89336	Notch 4	-2.2881933000
Y08409	Spot14	-2.2876898000
S81737	Alpha 1 syntrophin; Also: U40571	2.1638767000
D10495	Protein kinase C delta-type	2.1579099000

U48861	Beta 4 nicotinic acetylcholine receptor subunit	2.1518600000
M97935	Transcription factor ISGF-3 sequence; M97935	-2.2592952000
U37219	Cyclophilin-like protein CyP-60	-2.2589364000
AC002077	Cosmid clone LUCA17/3p213	2.1358956000
Z78289	(clone 1D2)/Z78289	2.1371687000
D55640	Monocyte pseudoautosomal boundary-like sequence	-2.2541249000
U31383	G protein gamma-10 subunit	-2.2559957000
U15131	p126 (ST5)	2.1301085000
U31875	Hep27 protein	-2.2477278000
X15331	Phosphoribosylpyrophosphate synthetase; D00860	2.1267157000
U65932	Extracellular matrix protein 1 (ECM1)	-2.2467447000
X67325	p27	-2.2399248000
M38258	Retinoic acid receptor gamma 1	2.1084635000
D50855	Calcium-sensing receptor; Also: U20760, U20759	-2.2251800000
HG2036-HT2090	Stimulatory Gdp/Gtp Exchange protein C-Ki-Ras P21	-2.2257614000
U40223	Uridine nucleotide receptor (UNR)	2.1007323000
U68723	Checkpoint suppressor 1	2.1021763000
M25322	Granule membrane protein-140	-2.2175497000
M94345	Macrophage capping protein	-2.2180100000
U89335	Notch 4	-2.2188636000
D78156	RasGTPase activating protein	2.0933341000
M33882	p78 protein	-2.2166936000
X99728	NDUFV3/X99728	-2.2137169000
***D16480	Mitochondrial enoylCoA hydratase	2.0832338000
Z49254	L23-related	-2.2020794000
Z26256	L-type calcium channel/Z26256	2.0780216000
X53683	LAG-1	-2.1972116000
HG2175-HT2245	Myosin, Heavy Polypeptide 10, Non-Muscle; Also: M69181	2.0730215000
D28423	Pre-splicing factor SRp20	2.0701672000
D87078	KIAA0235	2.0722131000
HG162-HT3165	Tyrosine Kinase Receptor Axl 2	2.0712927000
L78833	Lfp35 from BRCA1, Rho7 and vatl	2.0703335000
X17651	Myf-4 myogenic determination factor	-2.1869563000
X17254	TRANSCRIPTION FACTOR Eryf1	2.0632771000
HG3570-HT3773	Protein Phosphatase Inhibitor Homolog	-2.1780412000
U63336	MHC Class I region proline rich protein	-2.1787612000
X62573	RNA Fc receptor TC9	-2.1802693000
M27161	MHC class I CD8 alpha-chain (Leu-2/T8)	-2.1755118000
M58597	ELAM-1 ligand fucosyltransferase (ELFT)	-2.1774644000
S78085	PDCD2=programmed cell death-2/Rp8 homolog	-2.1691599000
D85939	p97 homolog	2.0528093000
U12139	Alpha1(XI) collagen (COL11A1)/U12139	2.0572285000
U83843	HIV-1 Nef interacting protein (Nip7-1)/U83843	2.0546131000
X99350	HFH4	2.0568858000
Z48519	XG (clone RACE5)/Z48519; Also: Z48518	2.0560468000
U48707	Protein phosphatase-1 inhibitor	-2.1658376000
U87964	Putative G-protein (GP-1)	-2.1662080000
U03270	Centrin	-2.1609185000
M96684	Pur (pur-alpha)	2.0450686000
U77968	Neuronal PAS1 (NPAS1)	2.0448728000
AF005037	Secretory carrier membrane protein (SCAMP1)	-2.1531286000

M68864	ORF	-2.1544240000
U24683	Anti-B cell autoantibody IgM heavy chain variable VDJ region	2.0397115000
X86018	MUF1 protein	2.0422801000
Z70220	Unknown protein (clone ICRFp507O0882)/Z70220	2.0423786000
HG1019-HT1019	Serine Kinase Psk-H1	-2.1511399000
HG3934-HT4204	G1 Phase-Specific	-2.1499116000
L49169	G0S3	-2.1515997000
D49490	Disulfide isomerase-related protein	-2.1380657000
D83783	KIAA0192	-2.1368790000
U45328	Ubiquitin-conjugating enzyme (UBE2I); Also: U31882	2.0229701000
M80563	CAPL protein	-2.1310570000
M94167	Heregulin-beta2	2.0207548000
M63573	Secreted cyclophilin-like protein (SCYLP)	2.0167254000
D14827	Tax helper protein 1	-2.1194209000
L24774	Delta3, delta2-CoA-isomerase; Also: Z25821_rna1, Z25820	2.0109336000
V00551	Alpha interferon	2.0107027000
X12433	pHS1-2 with ORF homolog to membrane receptor proteins	-2.1131910000
D42053	KIAA0091	2.0053307000
M58026	NB-1	2.0055666000
X93996	AFX prot	2.0044933000
U65011	Preferentially expressed antigen of melanoma (PRAME)	-2.1092410000
D30755	KIAA0113	-2.1044871000
S83308	SOX5=Sry-related HMG box	2.0011494000
Z18951	Caveolin	2.0024685000
Z48314	Apomucin; Also: U06711	1.9990217000
HG2290-HT2386	Calcitonin	-2.1007151000
L42354	Clone 48ES4/L42354	-2.1001120000
M28825	Thymocyte antigen CD1a	-2.0982975000
U40992	Heat shock protein hsp40 homolog	1.9974082000
U83192	Post-synaptic density protein 95 (PSD95)	1.9959202000
X70218	Protein phosphatase X	1.9929730000
Y08263	AAD14 protein	-2.0928083000
S34389	Heme oxygenase-2 [kidney 1627 nt]	-2.0891099000
L43579	Clone 110298/L43579; Also: L43575	1.9857183000
M80647	Thromboxane synthase	1.9832428000
Z31695	43 kDa inositol polyphosphate 5-phosphatase	1.9831751000
L38487	Estrogen receptor-related protein (hERRa1)	-2.0839503000
D50402	NRAMP1	1.9797759000
*M94250	Retinoic acid inducible factor (MK)	1.9788194000
*X64072	CD18; Also: M15395	1.9817507000
X93499	RAB7 prot	1.9775636000
J05582	Pancreatic mucin; Also: J05581	1.9740898000
S66431	RBP2=retinoblastoma binding protein 2	1.9738895000
U04343	CD86 antigen	-2.0770043000
X62153	P1 protein (P1.h); Also: D38073	-2.0763673000
X79066	ERF-1	-2.0739931000
AB000409	MNK1	-2.0695756000
J02947	Extracellular-superoxide dismutase (SOD3); Also: U10116	1.9665406000
M30185	Cholesteryl ester transfer protein	-2.0591846000
U31384	G protein gamma-11 subunit	-2.0615467000
M23294	Beta-hexosaminidase beta-subunit (HEXB)	1.9578227000

U18235	ATP-binding cassette protein (ABC2) HFBCD04 clone	1.9605421000
HG3731-HT4001	Ig Heavy Chain, Vdjrc Regions L23566	1.9552306000
M54951	Atrial natriuretic factor	1.9556397000
U20428	SNC19 sequence	1.9529377000
X63755	High-sulphur keratin	1.9523322000
X79483	ERK6 extracellular signal regulated kinase	1.9481684000
AF001294	IPL	-2.0447357000
U16031	TRANSCRIPTION FACTOR IL-4 Stat	-2.0447357000
X98833	Zinc finger protein, Hsal1	-2.0473722000
J04948	Alkaline phosphatase (ALP-1)	1.9444086000
X04898	Apolipoprotein AII	1.9464474000
X52896	Dermal fibroblast elastin; Also: HG2994-HT4851	1.9470905000
X56199	XIST a (locus DXS399E)	1.9455917000
X90872	gp25L2 protein	1.9451524000
HG4757-HT5207	Oncogene Mll-Af4, Fusion Activated; Also: L13773	-2.0424771000
U33839	Potassium channel/U33839	-2.0417873000
X99140	Hair keratin hHb5	1.9380942000
D88155	DNA for Ad4BP (SF-1); Also: U76388	-2.0367287000
M68840	Monoamine oxidase A (MAOA)	1.9351040000
U58032	Myotubularin related protein 1 (MTMR1)/U58032	1.9342459000
X70683	SOX-4 protein	1.9370161000
D82060	Kidney histidine rich putative membrane protein	-2.0292823000
J04056	Carbonyl reductase	-2.0295867000
S73813	CD39=lymphoid cell activation antigen	-2.0275535000
AF002224	E6-AP ubiquitin protein ligase 3A/promoter P1	1.9280628000
U13369	Ribosomal DNA repeating unit/U13369	1.9283702000
M19888	Small proline rich protein (sprl), clone 128	-2.0258177000
U63455	Sulfonylurea receptor (SUR1)	-2.0264311000
X69433	Mitochondrial isocitrate dehydrogenase (NADP+)	-2.0251010000
X13293	B-myb	1.9241500000
X71490	Vacuolar proton ATPase subunit D	1.9232699000
D84239	IgG Fc binding protein	-2.0197392000
L03840	Fibroblast growth factor receptor 4 (FGFR4); Also: X57205	-2.0213543000
*U57971	Calcium ATPase isoform 3x/a; Also: U60414	-2.0217060000
X68688	ZNF33B; Also: D31763	-2.0095571000
X16260	Inter-alpha-trypsin inhibitor subunit 3; Also: X69532_rna1	1.9108378000
U05040	FUSE binding protein	-2.0033528000
U83303	GCP-2 (granulocyte chemotactic protein-2)	-2.0065730000
X96698	D1075-like	-2.0043214000
HG2188-HT2258	Paired Box Hup1	1.9040931000
M55621	N-acetylglucosaminyltransferase I (GlcNAc-TI)	1.9061195000
*M85220	Heavy chain disease IgA chain CH3 region	1.9073097000
M92424	p53 associated MDM2	-1.9992393000
M76732	HOX7; Also: M97676	1.8986155000
M98447	Keratinocyte transglutaminase	-1.9956352000
U71364	Serine protase inhibitor (P19)	-1.9973864000
Y10514	CD152 protein/Y10514; Also: Y10508	-1.9929951000
D88146	UDP-galactose transporter 2	1.8931108000
U00928	Clone CE29 4.1 (CAC)n/(GTG)n repeat-containing	1.8961954000
U29615	Chitotriosidase precursor	1.8968843000
L05188	Small proline-rich protein 2 (SPRR2B)	-1.9881128000

D13988	Rab GDI	1.8898058000
M88282	Tactile protein	-1.9848647000
Z22548	Thiol-specific antioxidant protein	-1.9789790000
D87937	Alpha(1,2)fucosyltransferase 5	-1.9756311000
X78338	Synthetic adenovirus transformed retinal cell line MRP	-1.9770373000
HG3502-HT3696	Homeotic protein Hox54	1.8756978000
U33920	Clone lambda 5 semaphorin	1.8739306000
X82207	Beta-centractin (PC3)	-1.9657895000
U07882	Delta opioid receptor	1.8667303000
Y07565	RIN protein; Also: U71204	1.8655777000
AB000462	SH3 binding RES4-23A	-1.9614270000
HG3921-HT4191	Homeotic protein C6, Class I	-1.9577270000
J03909	Gamma-interferon-inducible protein (IP-30)	-1.9586833000
K02882	IGHD (Ig delta-chain); Also: K02882_2	-1.9580858000
U78180	Sodium channel 2 (hBNaC2)	-1.9604708000
U15197	Histo-blood group ABO protein	1.8577545000
D88795	Cadherin	-1.9559282000
M21984	(clone PWHTnT16) skeletal muscle Troponin T	-1.9555675000
U37248	Alpha-mannosidase (6A8)	-1.9553269000
X66401	LMP2 from TAP1, TAP2, LMP2, LMP7 and DOB	-1.9525503000
Z29083	5T4 Oncofetal antigen	-1.9550862000
M37075	Embryonic/atrial myosin light chain (MLC-1-emb/A isoform)	1.8536982000
U32576	Apolipoprotein apoC-IV (APOC4)	-1.9517017000
HG4557-HT4962	Small Nuclear Ribonucleoprotein U1, 1snrp	1.8495730000
L20859	Leukemia virus receptor 1 (GLVR1)	1.8480315000
L35240	Enigma	-1.9442358000
M21389	Keratin type II (58 kD)	-1.9454686000
U07919	Aldehyde dehydrogenase 6	-1.9452223000
U28687	Zinc finger containing protein ZNF157 (ZNF157)	-1.9474337000
U52154	G protein-coupled inwardly rectifying K+ channel Kir34	-1.9444827000
X07695	Cytokeratin 4	-1.9460836000
X89101	Fas (Apo-1, CD95)/X89101; Also: X83493, X63717, X83492	-1.9459607000
L40393	Clone S171	1.8411404000
M59916	Acid sphingomyelinase (ASM)	1.8401061000
M58603	Nuclear factor kappa-B DNA binding subunit (NF-kappa-B)	-1.9367650000
U02632	Calcium-activated potassium channel	-1.9338668000
L05500	Fetal brain adenylyl cyclase	1.8354686000
L37199	Clone cD24-1 Huntington's candidate region fragment	1.8371147000
S46622	Calcineurin A catalytic subunit	1.8343889000
U09411	Zinc finger protein ZNF132	-1.9281397000
U37519	Aldehyde dehydrogenase (ALDH8)	-1.9301847000
U80184	FLII	1.8287565000
L27071	Tyrosine kinase (TXK)	1.8251339000
X94453	Pyrroline 5-carboxylate synthetase	1.8253937000
D79985	KIAA0163	-1.9194703000
M54968	K-ras onco protein	-1.9203842000
U05340	p55CDC	-1.9212962000
U38480	Retinoid X receptor-gamma	-1.9189473000
*M13241	N-myc	1.8188182000
M13981	Inhibin A-subunit	1.8177636000

TABLE 10. Gene targets in heterogeneous MS spinal cord gray matter specimens.

Probe sets	Gene descriptions	Up (+) or down (-)
U70063	Acid ceramidase	+
X65644	MBP-2 MHC binding protein 2	+
X71129	Electron transfer flavoprotein beta subunit	-
L07515	Heterochromatin protein homolog (HP1)	-
U82671	HSP1-A from cosmids from Xq28	-
D49958	Membrane glycoprotein M6	+
X95404	Non-muscle type cofilin	-
**D78014	Dihydropyrimidinase related protein-3	+
X05997	Gastric lipase	-
M64108	Udulin 1	-
L48546	Tuberin (TSC2)	-
AB000381	GPI-anchored molecule-like, also D84290	-
D89859	Zinc finger 5 protein	-
*D10704	Choline kinase	+
*X64072	CD18; Also: M15395	+
X13916	LDL-receptor related protein	+
U37690	RNA polymerase II subunit (hsRPB10)	-
U12404	Csa-19	-
D13900	Mitochondrial short-chain enoyl-CoA hydratase	-
X62654	ME491/CD63 antigen	+
U34605	Retinoic acid- and interferon-inducible 58K prot RI58	-
M15395	Leukocyte adhesion protein (LFA-1/Mac-1) beta subunit	+
U20530	Bone phosphoprotein spp-24 precursor/U20530	-
U49785	D-dopachrome tautomerase	-
M76378	Cysteine-rich protein (CRP)	-
L19437	Transaldolase containing transposable element	-
X79683	Z68155 and others	+
M34079	HIV tat transactivator binding protein-1 (tbp-1)	-
U15197	Histo-blood group ABO protein	+
X69433	Mitochondrial isocitrate dehydrogenase (NADP+)	-
M58286	TNF receptor; Also: M63121, M33294, X55313, M75866	+
U58090	Hs-cul-4A	+
U01317	Beta-globin thalassemia from beta globin region	-
M92449	Human LTR	-
U09564	Serine kinase	-
U48437	Amyloid precursor-like protein 1	-
AC000099	Cosmid g0771a003	-
S95936	Transferrin	-
D26598	Proteasome subunit HsC10-II	-
D83243	NPAT	-
U06452	Melanoma antigen recognized by T-cells (MART-1)	-
U90716	Cell surface protein HCAR	-
X78992	ERF-2	+
U82256	Arginase type II	-
M35252	CO-029	-
J03068	DNF1552 (lung)	+
M64231	Spermidine synthase	-
HG1471-HT3923	Transcription Factor Oct-1a/1b; Also: X13403	-

L17131	High mobility group protein HMG-I(Y)	+
U94332	Osteoprotegerin (OPG)	-
U53204	Plectin (PLEC1)	+
U32581	Lambda/iota-protein kinase C-interacting protein	-
D78151	26S proteasome subunit p97	-
U59877	Low-Mr GTP-binding protein (RAB31); Also: U57091	+
U49974	Mariner2 transposable element/U49974	-
X99687	Methyl-CpG-binding protein 2 intron 2/X99687	-
AB002356	KIAA0358; Also: U77352	+
M75106	Prepro-plasma carboxypeptidase B	-
X99720	TPRC	+
U58675	Olfactory receptor cluster	+
L13800	Liver expressed protein/L13800	-
*D38583	Calgizzarin	+
L10413	Farnesyltransferase alpha-subunit	-
D82344	NBPhox	-
D38555	KIAA0079	+

TABLE 11. Gene targets in heterogeneous MS spinal cord white matter specimens

Probe sets	Gene descriptions	Up (+) or down (-)
Y09321	TAFII105	-
M15465	Pyruvate kinase type L; Also: D13243	-
U16120	Placental taurine transporter; Also: Z18956	-
U34976	Gamma-sarcoglycan	-
U53442	p38Beta MAP kinase	-
HG3570-HT3773	Protein Phosphatase Inhibitor Homolog	-
Z11793	Selenoprotein P	-
Z48501	Polyadenylate binding protein II/Z48501; Also: U68105	+
D28532	Renal Na+-dependent phosphate cotransporter	-
D28114	Myelin-associated oligodendrocytic basic protein	-
X69908	Mitochondrial ATP synthase c subunit (P2 form)	-
X92814	Rat HREV107-like protein	-
M62958	R degradation slow (RDS)	-
U40763	Clk-associated RS cyclophilin CARS-Cyp; Also: X99717	-
D00723	Hydrogen carrier protein	-
D90282	Carbamyl phosphate synthetase I	-
M73077	Glucocorticoid receptor repression factor 1 (GRF-1)	-
D87953	RTP	-
X15675	pTR7 repetitive sequence/X15675	-
AF009674	Axin	-
U06698	Neuronal kinesin heavy chain	-
AF000545	Putative purinergic receptor P2Y10	-
M20471	Brain-type clathrin light-chain a	-
AB000468	Zinc finger protein RES4-26	-
X00368	Prolactin 5/X00368	-
X97074	mRNS clathrin-associated protein	-
D90224	gp34	-
L11695	Activin receptor-like kinase (ALK-5)	-
M26880	Ubiquitin	-
X51602	Flt receptor-related tyrosine kinase	-

D00763	Proteasome subunit HC9	-
D38498	PMS5 (yeast PMS1 homolog)	-
U37690	RNA polymerase II subunit (hsRPB10)	-
X12530	B lymphocyte antigen CD20 (B1, Bp35); Also: X07203	-
D13413	Tumor-associated 120 kDa nuclear protein p120	-
Y00264	Amyloid A4 precursor of Alzheimer's disease	-
L19437	Transaldolase containing transposable element	-
L77864	Stat-like protein (Fe65)	-
Y10262	EYA3/Y10262; Also: U81602	-
X66534	Soluble guanylate cyclase large subunit	-
X04706	Homeobox (clone HHO.c13); Also: X17360_rna1	-
D79205	Ribosomal protein L39	-
HG3495-HT3689	Collagen Type Ix Alpha 1	-
U28369	Semaphorin V	-
U91618	Proneurotensin/proneuromedin N	-
L20941	Ferritin heavy chain	-
S59184	RYK=related to receptor tyrosine kinase	-
X17622	HBK2 potassium channel protein	-
X17025	Homolog of yeast IPP isomerase	-
U83461	Putative copper uptake protein (hCTR2)/U83461	-
U37359	MRE11 homolog hMRE11	-
U13395	Oxidoreductase (HHCMA56)	-
L07548	Aminoacylase-1 (ACY1)	-
U19247	Interferon-gamma receptor alpha chain	+
U11877	Interleukin-8 receptor type B (IL8RB)/U11877	-
M84605	Putative opioid receptor	-
M90657	Tumor antigen (L6)	-
M79462	PML-1	-
U28687	Zinc finger containing protein ZNF157 (ZNF157)	-
M13929	c-myc-P64; Also: HG3523-HT4900, HG3523-HT4899	-
M64929	Protein phosphatase 2A alpha subunit	+
HG2815-HT4023	Myosin, Light Chain/U02629; Also: HG2815-HT1357	-
Z50853	CLPP	-
L43338	Cadherin/L43338	-
U48959	Myosin light chain kinase (MLCK)	-
HG1614-HT1614	Protein Phosphatase 1 Alpha Catalytic Subunit	-
D17716	N-acetylglucosaminyltransferase V	-
Y00636	Lymphocyte function associated antigen-3 (LFA-3)	-
M27826	Endogenous retroviral protease	-
U32576	Apolipoprotein apoC-IV (APOC4)	-
L47276	Alpha topoisomerase/L47276; Also: L47277	-
L14787	DNA-binding protein	-
D63880	KIAA0159	-
U41060	Breast cancer estrogen regulated LIV-1 protein (LIV-1)	-
M62762	Vacuolar H+ ATPase proton channel subunit	-
D10922	FMLP-related receptor (HM63) -Also: M84562	-
M21984	Skeletal muscle Troponin T	-
**HG1877-HT1917	Myelin Basic protein; Also: M13577	+
X13546	Putative HMG-17 non-histone protein	+
HG2465-HT4871	Dna-Binding protein Ap-2 3	-

L03840	Fibroblast growth factor receptor 4 (FGFR4); X57205	-
U07151	GTP binding protein (ARL3)	-
Z68129	H-IDH NADH isocitrate dehydrogenase gamma	-
U69126	FUSE binding protein 2 (FBP2); Also: U94832	-
D50863	TESK1	-
AB002382	KIAA0384	-
X01703	Alpha-tubulin (b alpha 1)	-
L35249	Vacuolar H+-ATPase Mr 56,000 subunit (HO57); M60346	+
L36818	(clone 51C-3) 51C protein	-
L25119	Mu opiate receptor (MOR1)	-
M12125	Fibroblast muscle-type tropomyosin	-
X15822	COX VIIa-L liver-specific cytochrome c oxidase	-
M97347	Beta-1,6-N-acetylglucosaminyltransferase; L41415	-
D87258	Cancellous bone osteoblast serin protease	-
X95240	Cysteine-rich secretory protein-3; Also: X94323	-
D86962	KIAA0207	-
M57703	Melanin concentrating hormone (MCH); Also: S63697	-
X02874	(2'-5') oligo A synthetase E	-
L76159	FRG1	-
AB000220	Semaphorin E	-
M99487	Prostate-specific membrane Antigen	-
D85758	DROER homolog	+
X54637	Tyk2 non-receptor protein tyrosine kinase	+
U89335	Notch 4	-
X14684	La protein C-terminal region; Also: X13697, M20328	-
X99975	hRTR/hGCNF protein	-
AF005043	Poly(ADP-ribose) glycohydrolase (hPARG)	-
X76132	DCC	-
U50527	BRCA2 region, sequence CG018; Also: U57962	-
X74330	DNA primase (subunit p48)	-
M96326	Azurocidin	-
X55889	Ciliary neurotrophic factor 1	-
D28791	PIG-A	-
D78367	K12 keratin	-
D79997	KIAA0175	-
U02082	Guanine nucleotide regulatory protein (tim1)	-
AF001294	IPL	-
X63629	P cadherin	-
D82060	Kidney histidine rich putative membrane protein	-
D14822	CBFA2T1	-
D38437	DNA mismatch repair	-
M25322	Granule membrane protein-140	-
M84424	Cathepsin E (CTSE)	-
*M54927	Myelin proteolipid protein	-
X57351	1-8D from interferon-inducible family; HG1538-HT1538	-
U00952	Clone A9A2BRB7 (CAC)n/(GTG)n repeat-containing	+
D31766	KIAA0060	+
U03057	Actin bundling protein (HSN)	-
U65932	Extracellular matrix protein 1 (ECM1)	-
S87759	Protein phosphatase 2C alpha	-
HG2059-HT2114	Arrestin Beta 2	-

X77584	ATL-derived factor/thiredoxin	+
HG651-HT4201	Adducin Alpha Subunit 2	+
L10374	(clone CTG-A4) sequence	-
X85785	DARC	-
L77886	Protein tyrosine phosphatase	-
HG1980-HT2023	Tubulin, Beta 2	-
U28963	Gps2 (GPS2)	+
U78180	Sodium channel 2 (hBNaC2)	-
X78136	hnRNP-E2	+
X73460	Ribosomal protein L3	+
X60188	ERK1 protein serine/threonine kinase	-
M14058	Complement C1r	-
D30756	KIAA0049	-
U66061	TCRBC1 from germline T-cell receptor beta chain	-
X66436	Hsr1	-
X77753	TROP-2	-
U06233	POU domain protein (Brn-3b)	-
D28915	Hepatitis C-associated microtubular aggregate p44	-
M94556	mitochondrial specific ss-DNA binding protein	-
HG1019-HT1019	Serine Kinase Psk-H1	-
X66079	Spi-B	+
D83243	NPAT	-
HG846-HT846	Cyclophilin-Related protein	-
X96753	Melanoma-associated chondroitin sulfate proteoglycan	-
M13903	Involucrin	+
M13232	Factor VII serine protease precursor; Also: J02933	-
**L40027	Glycogen synthase kinase 3	-
Y00757	Polypeptide 7B2	-
U22398	Cdk-inhibitor p57KIP2 (KIP2)	-
L16464	ETS onco (PEP1)	-
U63336	MHC Class I region proline rich protein	-
M81601	Transcription elongation factor (SII)	+
AB000114	Osteomodulin	-
X83929	Type 3 desmocollin; Also: D17427	-
S73813	CD39=lymphoid cell activation antigen	-
U37219	Cyclophilin-like protein CyP-60	-
V00594	Metallothionein from cadmium-treated cells; J00271	-
D83542	Cadherin-15	-
M31520	Ribosomal protein S24; Also: HG3214-HT3391	-
U04343	CD86 antigen	-
X06272	Docking protein (signal recognition particle receptor)	+
U38964	PMS2 related (hPMSR2); Also: D38502	-
D31765	KIAA0061	-
D50477	Membrane-type matrix metalloproteinase 3; D83646	-
U51477	Diacylglycerol kinase zeta	-
X69920	Calcitonin receptor; Also: L00587	-
*D90086	Pyruvate dehydrogenase beta subunit	-
U41816	C-1	-
X05130	Prolyl 4-hydoxylase beta subunit; Also: J02783	+
AB000895	Cadherin FIB1	-
*D63135	ETS-like 30 kDa prot	-

U50330	Procollagen C-protase (pCP-2)	-
X89894	Nuclear receptor	-
U01691	Annexin V (ANX5) 5 -UTR; Also: X12454, M18366	+
U49957	LIM protein (LPP); Also: U49968	-
D21851	KIAA0028	-
HG4704-HT5146	Glial Growth Factor 2	-
D55640	Monocyte pseudoautosomal boundary-like sequence	-
D63874	HMG-1	-
L23333	Corticotropin releasing factor receptor; Also: X72304	+
U15131	p126 (ST5)	+
M83088	Phosphoglucomutase 1 (PGM1)	-
L42379	Bone-derived growth factor (BPGF-1)	-
AF005037	Secretory carrier membrane protein (SCAMP1)	-
J02947	Extracellular-superoxide dismutase (SOD3)	+
U12707	Wiskott-Aldrich syndrome protein (WASP); Also: U19927	+
Y10204	CD77 protein/Y10204	-
U19906	Arginine vasopressin receptor 1 (AVPR1)	-
HG3175-HT3352	Carcinoembryonic Antigen	-
X15306	NF-H 1	-
D63851	Unc-18 homolog	-
X64707	BBC1	-
M87339	Replication factor C 37-kDa subunit	+
X86809	Major astrocytic phosphoprotein PEA-15	-
J04164	Interferon-inducible protein 27-Sep	-
D14878	Protein D123	-
M93311	Metallothionein-III	-
U04520	Type IV collagen a5 chain (COL4A5)	-
X71129	Electron transfer flavoprotein beta subunit	-
L14837	Tight junction (zonula occludens) protein ZO-1	+
D16469	ORF Xq terminal portion	-
L11372	Protocadherin 43	-
X02751	N-ras	-
J03824	Uroporphyrinogen III synthase	+
S67798	PH-20	-
U16031	TRANSCRIPTION FACTORS IL-4 Stat	-
L43964	(clone F-T03796) STM-2	-
U79526	Orphan G-protein coupled receptor Dez isoform a	-
L10413	Farnesyltransferase alpha-subunit	-
HG3432-HT3621	Fibroblast Growth Factor Receptor K-Sam	-
M57466	MHC class II HLA-DP light chain; Also: M83664, X00532	+
D63876	KIAA0154	-
U07794	Tyrosine kinase (TXK)	-
X13839	Vascular smooth muscle alpha-actin	-
X07290	HF12	-
HG2264-HT2360	Atpase Ca2+ Transporting Plasma Membrane 1 6	-
U11037	Sel-1 like	+
D63475	KIAA0109	-
U44754	PSE-binding factor PTF gamma subunit	-
L78132	Prostate carcinoma tumor antigen (pcta-1)	-
D86977	KIAA0224	-
U83192	Post-synaptic density protein 95 (PSD95)	+

M21142	Guanine nucleotide-binding protein G-s-alpha-3; M21142	+
L41067	NF-AT4c	-
D26561	ORF E7 from papillomavirus 5b genome	-
U59111	Dermatan sulfate proteoglycan 3 (DSPG3)	-
HG2999-HT4756	Thyroid Peroxidase; Also: M25715	+
M62403	Insulin-like growth factor binding protein 4 (IGFBP4)	-
AB000115	Unknown protein	-
D90276	CGM7 nonspecific cross-reacting antigen (NCA)	-
M76424	Carbonic anhydrase VII (CA VII)	+
D31762	KIAA0057	-
L76568	S26 from excision and cross link repair protein (ERCC4)	-
X57579	Activin beta-A subunit (2); Also: J03634	+
X02404	Second calcitonin related peptide (CGRP)	-
Y10936	Hypothetical protein downstream of DMPK and DMAHP	-
D13643	KIAA0018	-
AF005361	Importin alpha 6	-
U41737	Pancreatic beta cell growth factor (INGAP)/U41737	-
K01383	Metallothionein-I-A	-
D80008	KIAA0186	-
AB002533	Qip1	-
U68135	SCC-S1c expressed in squamous cell cancer/U68135	-
X79353	XAP-4 GDP-dissociation inhibitor	-
D50310	Cyclin I	+
D15049	Protein tyrosine phosphatase	-
U31930	Deoxyuridine nucleotidohydrolase	-
M55543	Guanylate binding protein isom II (GBP-2)	-
M31303	Oncoprotein 18 (Op18)	-
U45328	Ubiquitin-conjugating enzyme (UBE2I); Also: U31882	+
L34657	Platelet/endothelial cell adhesion molecule-1 (PECAM-1)	+
U33818	Inducible poly(A)-binding protein	+
M16653	Pancreatic elastase IIB	-
U63825	Hepatitis delta antigen interacting protein A (dipA)	-
AB002318	KIAA0320	-
X66276	Skeletal muscle C-protein; Also: X73114	-
D13631	KIAA0006; Also: D25304	+
M91467	Serotonin receptor (5HT1E)	-
Z56281	Interferon regulatory factor 3	-
M37238	Phospholipase C; Also: X14034	+
X81003	HCG V	-
J00277	Lambda-[SK2-T2, HS578T]; RS-[3,4, 6]) c-Ha-ras1	-
L42373	Protein phosphatase 2A B56-alpha	-
J00210	IFNA (interferon alpha-d)	-
HG3523-HT4899	Proto-Oncogene C-Myc; Also: L00058, HG3523-HT4900	+
AF001548	815A9.1 myosin heavy chain from chromosome 16	-
L24774	Delta3, delta2-CoA-isomerase; Also: Z25821	+
Z48054	Peroxisomal targeting signal 1 (SKL type) receptor	-
D13720	LYK; Also: L10717	-
D87453	KIAA0264	-

TABLE 12. Gene targets found across all comparisons of MS gray matter spinal cord tissues against normal gray matter spinal cord tissues.*

Prob Set	G ne description	Mean fold change	Mean P value
*M87789	Hybridoma H210 anti-hepatitis A IgG V, C, CDR regions	3.0601579	0.000696592
*X64072	CD18; Also: M15395	1.8796121	0.00822973
M13207	Granulocyte-macrophage colony-stimulating factor (CSF1)	-2.063521	0.012103845
HG2709-HT2805	Serine/Threonine Kinase	1.6333372	0.016343018
M16707	Histone H4; clone FO108	-1.9707812	0.019372876

*Mean-fold change refers to the mean of the $\log_{10}$(ratio)-fold changes of all MS gray matter vs. normal gray matter comparisons for that gene; mean P value refers to the mean significance value of all MS gray matter vs normal gray matter comparisons for that gene-these parameters also apply to Tables 13-15.

TABLE 13. Gene targets found across all comparisons of MS white matter spinal cord tissues against normal white matter spinal cord tissues.

Probe Set	Gene description	Mean fold change	Mean P value
M84739	Autoantigen calreticulin	2.6243939	0.003487238
AB000895	Cadherin FIB1	-2.3163955	0.0055741
U12707	Wiskott-Aldrich syndrome protein (WASP); Also: U19927	2.2626829	0.005747785
*M63438	Ig rearranged gamma chain , V-J-C region; Also: X96754	3.0521967	0.006442657
U35234	Protein tyrosine phosphatase sigma	2.2824217	0.007725067
U37219	Cyclophilin-like protein CyP-60	-2.2580722	0.007876164
U45328	Ubiquitin-conjugating enzyme (UBE2I); Also: U31882	2.2253883	0.008423851
*M87789	Hybridoma H210 anti-hepatitis A IgG V, C, CDR regions	2.6095958	0.010125314
J02947	Extracellular-superoxide dismutase (SOD3)	2.1364149	0.012132355
X54637	Tyk2 non-receptor protein tyrosine kinase	2.0976451	0.012253421
*U37408	CtBP	2.09237	0.014673944
L24774	Delta3, delta2-CoA-isomerase; Also: Z25821_rna1	2.0763149	0.014787034
HG3033-HT3194	Spliceosomal protein Sap 62	2.2991536	0.015744522
U15131	p126 (ST5)	2.040288	0.016092199
*X64072	CD18; Also: M15395	2.0389044	0.018208883
HG162-HT3165	Tyrosine Kinase Receptor Axl 2	2.0291313	0.018333948
X15331	Phosphoribosylpyrophosphate synthetase subunit one	2.0054747	0.018860938
M96684	Pur (pur-alpha)	2.0364039	0.022166073
M23294	Beta-hexosaminidase beta-subunit (HEXB)	1.9720603	0.024128352
D42053	KIAA0091	1.9407077	0.024673169
U71364	Serine protase inhibitor (P19)	-1.9973864	0.026455898
U83192	Post-synaptic density protein 95 (PSD95)	1.8968397	0.026959056
M21984	(clone PWHTnT16) skeletal muscle Troponin T	-1.9555675	0.030792454

TABLE 14. Gene targets found across all comparisons of MS vs. normal spinal cord tissues, including gray and white matter comparisons.

Pr be Set	Gene description	Mean fold change	Mean P value
*M87789	Hybridoma H210 anti-hepatitis A IgG V, C, CDR regions	2.809845633	0.005934771
*X64072	CD18; Also: M15395	1.968107833	0.013773704

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TABLE 15. MS target genes commonly altered across MS spinal cord white matter samples that contain inflammatory cells and have evidence of demyelination.

Probe set	Gene description	Mean fold change	Mean P value
*M63438	Ig rearranged gamma chain , V-J-C region; Also: X96754	3.1649421	0.00019838
*M87789	Hybridoma H210 anti-hepatitis A IgG V, C, CDR regions	2.6612373	0.001353321
D26561	ORF E7 from papillomavirus 5b genome	-2.4064124	0.003085073
U22970	16-Jun (interferon-inducible peptide precursor)	-2.3853381	0.003506211
M84739	Autoantigen calreticulin	2.3988885	0.005304639
AB000895	Cadherin FIB1	-2.3152488	0.005469599
U45328	Ubiquitin-conjugating enzyme (UBE2I); Also: U31882	2.2473988	0.005664919
U12707	Wiskott-Aldrich syndrome protein (WASP); Also: U19927	2.236641	0.006397345
J04948	Alkaline phosphatase (ALP-1)	2.2390081	0.007089837
U37219	Cyclophilin-like protein CyP-60	-2.257496	0.0076284
J02947	Extracellular-superoxide dismutase (SOD3); U10116	2.1735344	0.008235838
X67325	p27	-2.2399248	0.00837286
U35234	Protein tyrosine phosphatase sigma	2.2315119	0.010160845
L41143	Expressed pseudo TCTA at t(1;3) translocation site	2.2002311	0.010868089
U12139	Alpha1(XI) collagen (COL11A1)/U12139	2.1197746	0.010952425
X54637	Tyk2 non-receptor protein tyrosine kinase	2.1068855	0.011617197
HG3033-HT3194	Spliceosomal protein Sap 62	2.3472607	0.012248234
HG162-HT3165	Tyrosine Kinase Receptor Axl 2	2.1075667	0.012419809
*X64072	CD18; Also: M15395	2.1152978	0.0127252
HG3945-HT4215	Phospholipid Transfer protein	2.3308357	0.013077384
U02619	TFIIIC Box B-binding subunit	2.2199388	0.013347355
X95406	Cyclin E	-2.1339379	0.013951429
L24774	Delta3, delta2-CoA-isomerase; Also: Z25821	2.0417176	0.015024809
M28825	Thymocyte antigen CD1a	-2.0982975	0.016299644
*U37408	CtBP	2.0620477	0.01643724
M23294	Beta-hexosaminidase beta-subunit (HEXB)	2.0583126	0.017046586
X07315	PP15 (placental protein 15)	2.0088193	0.017057852
D42053	KIAA0091	2.00626	0.017700929
U15131	p126 (ST5)	2.010507	0.018236373
U15655	Ets domain protein ERF	1.9931435	0.020560907
M61199	Cleavage signal 1 protein	1.981728	0.021409014
X93996	AFX protein	2.050328	0.023466008
X15331	Phosphoribosylpyrophosphate synthetase subunit one	1.926366	0.024012526
Z26256	L-type calcium channel	1.9508756	0.02443943
M36429	Transducin beta-2 subunit; Also: M16538	1.9340099	0.024855746
U71364	Serine protase inhibitor (P19)	-1.9973864	0.025176509
U83192	Post-synaptic density protein 95 (PSD95)	1.8899076	0.026517609

U33920	Clone lambda 5 semaphorin	1.8937119	0.028148796
U27333	Alpha (1,3) fucosyltransferase (FUT6), major transcript I	1.8809063	0.028243361
M96684	Pur (pur-alpha)	1.9775652	0.028255093
M21984	Clone PWHTnT16 skeletal muscle Troponin T	-1.9555675	0.029442849

TABLE 16. Genes previously reported to be dysregulated in MS central nervous system tissues.*

Probe set	Gene description	Up (+) or down (-)
U89606	Pyridoxal kinase	+
D10704	Choline kinase	+
X05610	Type IV collagen alpha-2 chain	+
M87789	Hybridoma H210 anti-hepatitis A IgG V, C, CDR regions	+
U18919	Chromosome 17q12-21 clone pOV-2	+
U16031	TRANSCRIPTION FACTOR IL-4 Stat	+
HG1595-HT4788	Heterogeneous Nuclear Ribonucleoprotein I; HG1595-HT4789	+
U21090	DNA polymerase delta small subunit	+
L26339	Autoantigen	+
U62317	Hypothetical protein 384D8_7	+
D38583	Calgizzarin	+
M13241	N-myc	+
L25270	XE169	+
U37408	CtBP	+
M63438	Ig rearranged gamma chain , V-J-C region; Also: X96754	+
L05624	MAP kinase kinase; Also: L11284	+
U52518	Grb2-related adaptor protein (Grap)	+
U64573	Connexin43 gap junction prot (connexin43)/U64573	+
M35999	Platelet glycoprotein IIIa (GPIIIa)	+
X13334	CD14 myeloid cell-specific leucine-rich glycoprotein	+
M94250	Retinoic acid inducible factor (MK)	+
M85220	Heavy chain disease IgA chain CH3 region	+

X57809	Rearranged Ig lambda light chain; S42404	+
HG2730-HT2828	Fibrinogen, A Alpha Polypeptide; Also: M58569	+
D84145	WS-3	-
M11749	Thy-1 glycoprotein	-
U28811	Cysteine-rich fibroblast growth factor receptor (CFR-1)	-
S82024	SCG10=neuron-specific growth-associated protein/stathmin homolog	-
M74826	Glutamate decarboxylase (GAD-2)	-
D90086	Pyruvate dehydrogenase beta subunit	-
D61391	Phosphoribosypyrophosphate synthetase-associated protein 39	-
X00734	Beta-tubulin (5-beta) with ten Alu family members	-
U57971	Calcium ATPase isoform 3x/a; Also: U60414	-
M54927	Myelin proteolipid protein	-
X63578	Parvalbumin	-
X07109	Protein kinase C (PKC) type beta II	-
D63135	ETS-like 30 kDa protein	-
J03263	Lysosome-associated membrane glycoprotein (lamp A)	-
D13988	Rab GDI	-
M58459	Ribosomal protein (RPS4Y) isom	-
U60269	Putative ERVK envelope protein	-
Y12711	Putative progesterone binding protein	-

* - These genes, denoted in Tables 1-15 by only one asterisk, are being shown for the purpose of (a) validation of the methodology of the present invention, and (b) for use as targets in combination with other genes found to be dysregulated by the inventors. The probe set identifiers for some of these genes (*i.e.*, Ig lambda light chain and Heavy chain disease IgA chain CH3 region) were not mentioned in the report by Lock *et al.* (2002). The probe set identifier for fibrinogen (HG2730-HT2828) was not identical to the probe set in the report by Lock *et al.* (2002) (HG2730-HT2827).

Table 17. Genes previously reported to be dysregulated in MS brain lesions using high throughput sequencing of cDNA libraries (Chabas *et al.*, *Science* 2001; 294: 1731-5) and also shown by the inventors to be similarly dysregulated in MS spinal cords, using DNA microarrays.**

Probe set	Gene Name	Up (+) or Down (-)
D78014	Dihydropyrimidinase related protein-3	+
HG1877-HT1917	Myelin Basic Protein	+
X05299	Major centromere autoantigen CENP-B	+
L40027	Glycogen synthase kinase 3	-

** - These genes, denoted in Tables 1-15 by two asterisks, are being shown for the purpose of (a) validation of the methodology of the present invention, and (b) for use as targets in combination with other genes found to be dysregulated by the inventors. Dihydropyrimidinase related protein-3 shares the probe set number identifier with the report by Chabas *et al.* (2001). The designation HG1877-HT1917 is a probe set identifier provided by Affymetrix. The probe set identifiers for Major centromere autoantigen CENP-B (X05299) and Glycogen synthase kinase 3 (L40027) are not identical to those reported by Chabas et al. for these genes.

Table 18. Genes previously reported to be dysregulated in MS brain lesions using filter cDNA microarrays (Whitney *et al.*, *Annals of Neurology*, 1999; 46(3):425-8), and also shown by the inventors to be similarly dysregulated in MS spinal cords, using DNA microarrays.***

Probe set	Gene Name	Up (+) or Down (-)
D16480	Mitochondrial enoylCoA hydratase	+
J05037	Serine dehydratase	+

*** - These genes, denoted in Tables 1-15 by three asterisks, are being shown for the purpose of (a) validation of the methodology of the present invention, and (b) for use as targets in combination with other genes found to be dysregulated by the inventors. The gene identifiers reported by Whitney *et al.* (1999) (75860 for Mitochondrial enoylCoA hydratase and 76751 for serine dehydratase) differ from the probe set identifiers shown above.

III. Gene Therapy

Thus, in accordance with the present invention, there are provided methods for the treatment of MS by gene therapy. Such methods include both the administration of a gene therapy vector encoding one or more genes identified as being downregulated in MS, and for genes that are overexpressed in MS, transgenes may be provided that reduce expression of appropriate targets.

MS is an inflammatory disease of the central nervous system. Entry of immune cells into the perivascular tissues of the brain and spinal cord lead to loss of myelin and eventually to

axonal loss and neurodegeneration. In some cases, axonal loss occurs during the early stages of formation of the MS lesions. The molecules that mediate this tissue damage (*i.e.*, from activated immune cells or from the affected tissues themselves) can be targeted with various therapies, to attempt to revert the ongoing demyelination or loss of axons. For instance, in Table 1, multiple genes are found to have elevated expression in MS tissues. Glutamate excitotoxicity has been linked to MS. Excitatory amino acid transporters and receptors, as well as calcium entry into the cells mediated by calcium channels, are mechanisms involved in glutamate toxicity. The metabotropic glutamate receptor 4 (probe set U92457) and the excitatory amino acid transporter 4 (U18244) are found to be elevated. Similarly, the P/Q-type calcium channel alpha 1 subunit was elevated. Among the inflammatory genes that are found to be elevated, complement component 2 (L09708), Ig-like transcript 2 (U82279), interleukin 8 receptor type B (U11877), Ig heavy chain VDJC region (HG4458-HT4727), monocyte chemoattractant protein-4 precursor (U46767), phospholipase A2 (M21056), granulocyte colony-stimulating factor receptor (CSF3R) (M59820) are found to be upregulated and would thus be considered targets for downregulation in MS. In contrast, the 5-HT6 serotonin receptor (L41147), and the STAT2 transcription factor (U18671) are downregulated, and therefore we propose that attempts to upregulate these transcripts will benefit MS patients. Similar examples of target selection can be extracted from Tables 2-10.

In Table 2, examples of target genes that are upregulated in MS spinal cords include the inflammation related genes Anti-hepatitis A IgG (*M87789) and the metal ion-related NRAMP1 (D50402). Downregulated genes that could be targeted for treating MS include the neurofilament triplet protein L (U57341), involved in neuronal cytoskeletal integrity, and a lymphoid specific transcription factor (M36542).

In Table 3, examples of target genes that are upregulated in MS spinal cords include the inflammation related genes CD14 (*X13334), C5a anaphylatoxin receptor (M62505), Fc receptor Iib3 for IgG (Affymetrix designation HG491-HT491), lymph node homing receptor (M25280), and the complement component properdin (M83652). Also in Table 3, downregulated genes that could be used as targets of treatment include guanylate kinase (L76200) involved in DNA repair, and mitochondrial creatine kinase (J04469) involved in energy metabolism.

In Table 4, elevated transcripts for the inflammation-related genes cathepsin C (X87212), T cell receptor zeta chain (J04132), and MHC class II HLA (M96132) may serve as targets of

treatment. From Table 5, elevated phospholipid transfer protein (HG3945-HT4215), and downregulated transcripts for the DNA mismatch repair gene MLH1 (AF001359) and the glutamate transporter EAAT3 (U08989) are candidate targets. From Table 6, the downregulated TGF-beta superfamily protein (AB000584) may be used as a example. From Table 7, the repair gene Rad23A homolog (AD000092) was also downregulated. From Table 8, the apoptosis-related phospholipid scramblase (AF008445) is found to be an elevated target transcript. From Table 9, the inhibitor of apoptosis protein 1 (U45878) is downregulated, and elevation of its expression could prevent (neuronal) cell death. The immune attenuator CD152/CTLA4 (Y10514) is also downregulated, and elevation of its expression could attenuate inflammation in MS. The checkpoint suppressor 1 (U68723) is also found to be elevated. From Table 10, upregulated transcripts that are hereby proposed as targets of MS treatments include acid ceramidase (U70063), the MHC-binding protein 2 MBP2 (X65644), and choline kinase (*D10704). Also, from Table 11, decreased mitochondrial ATP synthase (X69908), and increased interferon γ (IFN-γ) receptor α chain (U19247) can be used as targets of treatment. A similar approach can be implemented for selecting genes from Tables 12 to 15.

The above genes are mentioned only by way of example, for a concept of treating MS that can be applied to all other genes in the list. Various aspects of gene delivery and expression are set forth below.

1. Therapeutic Transgenes

Thus, in accordance with the present invention, there are provided methods of treating and preventing MS utilizing genes identified as being overexpressed or underexpressed in MS, as illustrated in Tables 1-15. By inhibiting or increasing the expression of various of these genes, therapeutic benefit may be provided to patients.

2. Antisense

In contrast to "replacement" gene therapy, described above, it may be desirable to down-regulate the expression of certain targets that are overexpressed in individuals afflicted with, or at risk of, MS. A variety of mechanisms are available for effecting a decrease in gene expression using genetic constructs.

The term "antisense" nucleic acid refers to oligo- and polynucleotides complementary to bases sequences of a target DNA or RNA. When introduced into a cell, antisense molecules hybridize to a target nucleic acid and interfere with its transcription, transport, processing, splicing or translation. Targeting double-stranded DNA leads to triple helix formation; targeting RNA will lead to double helix formation.

Antisense constructs may be designed to bind to the promoter or other control regions, exons, introns or even exon-intron boundaries of a gene. Antisense RNA constructs, or DNA encoding such antisense RNA's, may be employed to inhibit gene transcription or translation within a host cell. Nucleic acid sequences which comprise "complementary nucleotides" are those which are capable of base-pairing according to the standard Watson-Crick complementarity rules. That is, that the larger purines will base pair with the smaller pyrimidines to form combinations of guanine paired with cytosine (G:C) and adenine paired with either thymine in the case of DNA (A:T), or uracil (A:U) in the case of RNA. Inclusion of less common bases such as inosine, 5-methylcytosine, 6-methyladenine, hypoxanthine and others in hybridizing sequences does not interfere with pairing.

As used herein, the terms "complementary" and "antisense sequences" mean nucleic acid sequences that are substantially complementary over their entire length and have very few base mismatches. For example, nucleic acid sequences of fifteen bases in length may be termed complementary when they have complementary nucleotides at thirteen or fourteen positions. Naturally, nucleic acid sequences which are "completely complementary" will be nucleic acid sequences which have perfect base pair matching with the target sequences, *i.e.*, no mismatches. Other sequences with lower degrees of homology are contemplated. For example, an antisense construct with limited regions of high homology, but overall containing a lower degree (50% or less) total homology, may be used.

While all or part of the gene sequence may be employed in the context of antisense construction, statistically, any sequence of 17 bases long should occur only once in the human genome and, therefore, suffice to specify a unique target. Although shorter oligomers are easier to make and increase *in vivo* accessibility, numerous other factors are involved in determining the specificity of hybridization. Both binding affinity and sequence specificity of an oligonucleotide to its complementary target increases with increasing length. It is contemplated that oligonucleotides of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more base pairs will be

used. One can readily determine whether a given antisense nucleic acid is effective at targeting a gene simply by testing the construct *in vitro* to determine whether the gene's function or expression is affected.

In certain embodiments, one may wish to employ antisense constructs which include other elements, for example, those which include C-5 propyne pyrimidines. Oligonucleotides which contain C-5 propyne analogs of uridine and cytidine have been shown to bind RNA with high affinity and to be potent inhibitors or gene expression. Wagner *et al.* (1993).

3. Ribozymes

The term "ribozyme" refers to an RNA-based enzyme capable of targeting and cleaving particular DNA and RNA sequences. Ribozymes can either be targeted directly to cells, in the form of RNA oligonucleotides incorporating ribozyme sequences, or introduced into the cell as an expression construct encoding the desired ribozymal RNA. Ribozymes may be used and applied in much the same way as described for antisense nucleic acids. Ribozyme sequences also may be modified in much the same way as described for antisense nucleic acids. For example, one could include modified bases or modified phosphate backbones to improve stability or function.

4. RNA Interference

RNA interference (RNAi) is a form of gene silencing triggered by double-stranded RNA (dsRNA). DsRNA activates post-transcriptional gene expression surveillance mechanisms that appear to function to defend cells from virus infection and transposon activity. Fire *et al.* (1998); Grishok *et al.* (2000); Ketting *et al.* (1999); Lin & Avery (1999); Montgomery *et al.* (1998); Sharp (1999); Sharp & Zamore (2000); Tabara *et al.* (1999). Activation of these mechanisms targets mature, dsRNA-complementary mRNA for destruction. RNA_i offers major experimental advantages for study of gene function. These advantages include a very high specificity, ease of movement across cell membranes, and prolonged down-regulation of the targeted gene. Fire *et al.* (1998); Grishok *et al.* (2000); Ketting *et al.* (1999); Lin & Avery (1999); Montgomery *et al.* (1998); Sharp (1999); Sharp & Zamore (2000); Tabara *et al.* (1999). Moreover, dsRNA has been shown to silence genes in a wide range of systems, including plants, protozoans, fungi, *C.*

elegans, *Trypanosoma* and *Drosophila*. Grishok *et al.* (2000); Sharp (1999); Sharp & Zamore (1999).

Several principles are worth note (see Plasterk & Ketting, 2000) First, the dsRNA should be directed to an exon, although some exceptions to this rule have been shown. Second, a homology threshold (probably about 80-85% over 200 bases) is required. Most tested sequences are 500 base pairs or greater. Third, the targeted mRNA is lost after RNA_i. Fourth, the effect is non-stoichometric, and thus incredibly potent. In fact, it has been estimated that only a few copies of dsRNA are required to knock down >95% of targeted gene expression in a cell. Fire *et al.* (1998). Recently, shorter (~20 base pairs) synthetic duplex RNAs have been shown to efficiently perform RNAi, by using liposome transfection. Further, similar short interfering RNA (siRNA) duplexes of 19-25 base pairs have been used by transfection via recombinant DNA constructs containing a promoter for U6 small nuclear RNA (snRNA) to drive nuclear expression of a single RNA transcript. This is also known as the hairpin siRNA/suppression of endogenous RNA (SUPER) strategy and has been shown to eliminate the expression of a target gene in long-term mammalian cell cultures (Brummelkamp *et al.*, 2002; Paul *et al.*, 2002; Lee *et al.*, 2002; Miyagishi *et al.*, 2002).

Although the precise mechanism of RNA_i is still unknown, the involvement of permanent gene modification or the disruption of transcription have been experimentally eliminated. It is now generally accepted that RNA_i acts post-transcriptionally, targeting RNA transcripts for degradation. It appears that both nuclear and cytoplasmic RNA can be targeted. Bosher and Labouesse (2000).

5. Single Chain Antibodies

Naturally-occurring antibodies (of isotype IgG) produced by B cells, consist of four polypeptide chains. Two heavy chains (composed of four immunoglobulin domains) and two light chains (made up of two immunoglobulin domains) are held together by disulphide bonds. The bulk of the antibody complex is made up of constant immunoglobulin domains. These have a conserved amino acid sequence, and exhibit low variability. Different classes of constant regions in the stem of the antibody generate different isotypes of antibody with differing properties. The recognition properties of the antibody are carried by the variable regions (VH and VL) at the ends of the arms. Each variable domain contains three hypervariable regions

known as complementarity determining regions, or CDRs. The CDRs come together in the final tertiary structure to form an antigen binding pocket. The human genome contains multiple fragments encoding portions of the variable domains in regions of the immunoglobulin gene cluster known as V, D and J. During B cell development these regions undergo recombination to generate a broad diversity of antibody affinities. As these B cell populations mature in the presence of a target antigen, hypermutation of the variable region takes place, with the B cells producing the most active antibodies being selected for further expansion in a process known as affinity maturation.

A major breakthrough was the generation of monoclonal antibodies, pure populations of antibodies with the same affinity. This was achieved by fusing B cells taken from immunized animals with myeloma cells. This generates a population of immortal hybridomas, from which the required clones can be selected. Monoclonal antibodies are very important research tools, and have been used in some therapies. However, they are very expensive and difficult to produce, and if used in a therapeutic context, can elicit and immune response which will destroy the antibody. This can be reduced in part by humanizing the antibody by grafting the CDRs from the parent monoclonal into the backbone of a human IgG antibody. It may be better to deliver antibodies by gene therapy, as this would hopefully provide a constant localized supply of antibody following a single dose of vector. The problems of vector design and delivery are dealt with elsewhere, but antibodies in their native form, consisting of two different polypeptide chains which need to be generated in approximately equal amounts and assembled correctly are not good candidates for gene therapy. However, it is possible to create a single polypeptide which can retain the antigen binding properties of a monoclonal antibody.

The variable regions from the heavy and light chains (VH and VL) are both approximately 110 amino acids long. They can be linked by a 15 amino acid linker (*e.g.*, $(glycine_4serine)_3$), which has sufficient flexibility to allow the two domains to assemble a functional antigen binding pocket. Addition of various signal sequences allows the scFv to be targeted to different organelles within the cell, or to be secreted. Addition of the light chain constant region (Ck) allows dimerization via disulphide bonds, giving increased stability and avidity. However, there is evidence that scFvs spontaneously multimerize, with the extent of aggregation (presumably via exposed hydrophobic surfaces) being dependent on the length of the glycine-serine linker.

The variable regions for constructing the scFv are obtained as follows. Using a monoclonal antibody against the target of interest, it is a simple procedure to use RT-PCR to clone out the variable regions from mRNA extracted from the parent hybridoma. Degenerate primers targeted to the relatively invariant framework regions can be used. Expression constructs are available with convenient cloning sites for the insertion of the cloned variable regions.

6. Vectors

In accordance with the present invention, both stimulatory and inhibitory genes may be provided to cells of an MS patient and expressed therein. Stimulatory genes are generally simply copies of the gene of interest, although in some cases they may be genes, the expression of which direct the expression of the gene of interest. Inhibitory genes, discussed above, may include antisense or single-chain antibody genes.

The term "vector" is used to refer to a carrier nucleic acid molecule into which a nucleic acid sequence can be inserted for introduction into a cell where it can be replicated. A nucleic acid sequence can be "exogenous," which means that it is foreign to the cell into which the vector is being introduced or that the sequence is homologous to a sequence in the cell but in a position within the host cell nucleic acid in which the sequence is ordinarily not found. Vectors include plasmids, cosmids, viruses (bacteriophage, animal viruses, and plant viruses), and artificial chromosomes (*e.g.*, YACs). One of skill in the art would be well equipped to construct a vector through standard recombinant techniques (see, for example, Maniatis *et al.*, 1989 and Ausubel *et al.*, 1994, both incorporated herein by reference).

The term "expression vector" refers to any type of genetic construct comprising a nucleic acid coding for a RNA capable of being transcribed. In some cases, RNA molecules are then translated into a protein, polypeptide, or peptide. In other cases, these sequences are not translated, for example, in the production of antisense molecules or ribozymes. Expression vectors can contain a variety of "control sequences," which refer to nucleic acid sequences necessary for the transcription and possibly translation of an operably linked coding sequence in a particular host cell. In addition to control sequences that govern transcription and translation, vectors and expression vectors may contain nucleic acid sequences that serve other functions as well and are described *infra.*

a. Promoters and Enhancers

A "promoter" is a control sequence that is a region of a nucleic acid sequence at which initiation and rate of transcription are controlled. It may contain genetic elements at which regulatory proteins and molecules may bind, such as RNA polymerase and other transcription factors, to initiate the specific transcription of a nucleic acid sequence. The phrases "operatively positioned," "operatively linked," "under control," and "under transcriptional control" mean that a promoter is in a correct functional location and/or orientation in relation to a nucleic acid sequence to control transcriptional initiation and/or expression of that sequence.

A promoter generally comprises a sequence that functions to position the start site for RNA synthesis. The best known example of this is the TATA box, but in some promoters lacking a TATA box, such as, for example, the promoter for the mammalian terminal deoxynucleotidyl transferase gene and the promoter for the SV40 late genes, a discrete element overlying the start site itself helps to fix the place of initiation. Additional promoter elements regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 bp upstream of the start site, although a number of promoters have been shown to contain functional elements downstream of the start site as well. To bring a coding sequence "under the control of" a promoter, one positions the 5′ end of the transcription initiation site of the transcriptional reading frame "downstream" of (*i.e.*, 3′ of) the chosen promoter. The "upstream" promoter stimulates transcription of the DNA and promotes expression of the encoded RNA.

The spacing between promoter elements frequently is flexible, so that promoter function is preserved when elements are inverted or moved relative to one another. In the tk promoter, the spacing between promoter elements can be increased to 50 bp apart before activity begins to decline. Depending on the promoter, it appears that individual elements can function either cooperatively or independently to activate transcription. A promoter may or may not be used in conjunction with an "enhancer," which refers to a cis-acting regulatory sequence involved in the transcriptional activation of a nucleic acid sequence.

A promoter may be one naturally associated with a nucleic acid sequence, as may be obtained by isolating the 5′ non-coding sequences located upstream of the coding segment and/or exon. Such a promoter can be referred to as "endogenous." Similarly, an enhancer may be one naturally associated with a nucleic acid sequence, located either downstream or upstream of that

sequence. Alternatively, certain advantages will be gained by positioning the coding nucleic acid segment under the control of a recombinant or heterologous promoter, which refers to a promoter that is not normally associated with a nucleic acid sequence in its natural environment. A recombinant or heterologous enhancer refers also to an enhancer not normally associated with a nucleic acid sequence in its natural environment. Such promoters or enhancers may include promoters or enhancers of other genes, and promoters or enhancers isolated from any other virus, or prokaryotic or eukaryotic cell, and promoters or enhancers not "naturally occurring," *i.e.*, containing different elements of different transcriptional regulatory regions, and/or mutations that alter expression. For example, promoters that are most commonly used in recombinant DNA construction include the β-lactamase (penicillinase), lactose and tryptophan (trp) promoter systems. In addition to producing nucleic acid sequences of promoters and enhancers synthetically, sequences may be produced using recombinant cloning and/or nucleic acid amplification technology, including PCR™, in connection with the compositions disclosed herein (see U.S. Patent 4,683,202 and 5,928,906, each incorporated herein by reference). Furthermore, it is contemplated the control sequences that direct transcription and/or expression of sequences within non-nuclear organelles such as mitochondria, chloroplasts, and the like, can be employed as well.

Naturally, it will be important to employ a promoter and/or enhancer that effectively directs the expression of the DNA segment in the organelle, cell type, tissue, organ, or organism chosen for expression. Those of skill in the art of molecular biology generally know the use of promoters, enhancers, and cell type combinations for protein expression, (see, for example Sambrook *et al.* 1989, incorporated herein by reference). The promoters employed may be constitutive, tissue-specific, inducible, and/or useful under the appropriate conditions to direct high level expression of the introduced DNA segment, such as is advantageous in the large-scale production of recombinant proteins and/or peptides. The promoter may be heterologous or endogenous.

Additionally any promoter/enhancer combination (as per, for example, the Eukaryotic Promoter Data Base EPDB, www.epd.isb-sib.ch/) could also be used to drive expression. Use of a T3, T7 or SP6 cytoplasmic expression system is another possible embodiment. Eukaryotic cells can support cytoplasmic transcription from certain bacterial promoters if the appropriate

bacterial polymerase is provided, either as part of the delivery complex or as an additional genetic expression construct.

Table 19 lists non-limiting examples of elements/promoters that may be employed, in the context of the present invention, to regulate the expression of a RNA. Table 20 provides non-limiting examples of inducible elements, which are regions of a nucleic acid sequence that can be activated in response to a specific stimulus.

TABLE 19

Promoter and/or Enhancer

Promoter/Enhancer	References
Immunoglobulin Heavy Chain	Banerji *et al.*, 1983; Gilles *et al.*, 1983; Grosschedl *et al.*, 1985; Atchinson *et al.*, 1986, 1987; Imler *et al.*, 1987; Weinberger *et al.*, 1984; Kiledjian *et al.*, 1988; Porton *et al.*; 1990
Immunoglobulin Light Chain	Queen *et al.*, 1983; Picard *et al.*, 1984
T-Cell Receptor	Luria *et al.*, 1987; Winoto *et al.*, 1989; Redondo *et al.*; 1990
HLA DQ a and/or DQ β	Sullivan *et al.*, 1987
β-Interferon	Goodbourn *et al.*, 1986; Fujita *et al.*, 1987; Goodbourn *et al.*, 1988
Interleukin-2	Greene *et al.*, 1989
Interleukin-2 Receptor	Greene *et al.*, 1989; Lin *et al.*, 1990
MHC Class II 5	Koch *et al.*, 1989
MHC Class II HLA-Dra	Sherman *et al.*, 1989
β-Actin	Kawamoto *et al.*, 1988; Ng *et al.*; 1989
Muscle Creatine Kinase (MCK)	Jaynes *et al.*, 1988; Horlick *et al.*, 1989; Johnson *et al.*, 1989
Prealbumin (Transthyretin)	Costa *et al.*, 1988
Elastase I	Ornitz *et al.*, 1987
Metallothionein (MTII)	Karin *et al.*, 1987; Culotta *et al.*, 1989
Collagenase	Pinkert *et al.*, 1987; Angel *et al.*, 1987
Albumin	Pinkert *et al.*, 1987; Tronche *et al.*, 1989, 1990
α-Fetoprotein	Godbout *et al.*, 1988; Campere *et al.*, 1989

TABLE 19 Promoter and/or Enhancer	
Promoter/Enhancer	References
γ-Globin	Bodine *et al.*, 1987; Perez-Stable *et al.*, 1990
β-Globin	Trudel *et al.*, 1987
c-fos	Cohen *et al.*, 1987
c-HA-*ras*	Triesman, 1986; Deschamps *et al.*, 1985
Insulin	Edlund *et al.*, 1985
Neural Cell Adhesion Molecule (NCAM)	Hirsch *et al.*, 1990
α_1-Antitrypsin	Latimer *et al.*, 1990
H2B (TH2B) Histone	Hwang *et al.*, 1990
Mouse and/or Type I Collagen	Ripe *et al.*, 1989
Glucose-Regulated Proteins (GRP94 and GRP78)	Chang *et al.*, 1989
Rat Growth Hormone	Larsen *et al.*, 1986
Human Serum Amyloid A (SAA)	Edbrooke *et al.*, 1989
Troponin I (TN I)	Yutzey *et al.*, 1989
Platelet-Derived Growth Factor (PDGF)	Pech *et al.*, 1989
Duchenne Muscular Dystrophy	Klamut *et al.*, 1990
SV40	Banerji *et al.*, 1981; Moreau *et al.*, 1981; Sleigh *et al.*, 1985; Firak *et al.*, 1986; Herr *et al.*, 1986; Imbra *et al.*, 1986; Kadesch *et al.*, 1986; Wang *et al.*, 1986; Ondek *et al.*, 1987; Kuhl *et al.*, 1987; Schaffner *et al.*, 1988
Polyoma	Swartzendruber *et al.*, 1975; Vasseur *et al.*, 1980; Katinka *et al.*, 1980, 1981; Tyndell *et al.*, 1981; Dandolo *et al.*, 1983; de Villiers *et al.*, 1984; Hen *et al.*, 1986; Satake *et al.*, 1988; Campbell and/or Villarreal, 1988
Retroviruses	Kriegler *et al.*, 1982, 1983; Levinson *et al.*, 1982; Kriegler *et al.*, 1983, 1984a, b, 1988; Bosze *et al.*, 1986; Miksicek *et al.*, 1986; Celander *et al.*, 1987; Thiesen *et al.*, 1988; Celander *et al.*, 1988; Choi *et al.*, 1988; Reisman *et al.*, 1989

TABLE 19 Promoter and/or Enhancer	
Promoter/Enhancer	References
Papilloma Virus	Campo *et al.*, 1983; Lusky *et al.*, 1983; Spandidos and/or Wilkie, 1983; Spalholz *et al.*, 1985; Lusky *et al.*, 1986; Cripe *et al.*, 1987; Gloss *et al.*, 1987; Hirochika *et al.*, 1987; Stephens *et al.*, 1987
Hepatitis B Virus	Bulla *et al.*, 1986; Jameel *et al.*, 1986; Shaul *et al.*, 1987; Spandau *et al.*, 1988; Vannice *et al.*, 1988
Human Immunodeficiency Virus	Muesing *et al.*, 1987; Hauber *et al.*, 1988; Jakobovits *et al.*, 1988; Feng *et al.*, 1988; Takebe *et al.*, 1988; Rosen *et al.*, 1988; Berkhout *et al.*, 1989; Laspia *et al.*, 1989; Sharp *et al.*, 1989; Braddock *et al.*, 1989
Cytomegalovirus (CMV)	Weber *et al.*, 1984; Boshart *et al.*, 1985; Foecking *et al.*, 1986
Gibbon Ape Leukemia Virus	Holbrook *et al.*, 1987; Quinn *et al.*, 1989

TABLE 20 Inducible Elements		
Element	Inducer	References
MT II	Phorbol Ester (TFA) Heavy metals	Palmiter *et al.*, 1982; Haslinger *et al.*, 1985; Searle *et al.*, 1985; Stuart *et al.*, 1985; Imagawa *et al.*, 1987, Karin *et al.*, 1987; Angel *et al.*, 1987b; McNeall *et al.*, 1989
MMTV (mouse mammary tumor virus)	Glucocorticoids	Huang *et al.*, 1981; Lee *et al.*, 1981; Majors *et al.*, 1983; Chandler *et al.*, 1983; Lee *et al.*, 1984; Ponta *et al.*, 1985; Sakai *et al.*, 1988
β-Interferon	Poly(rI)x Poly(rc)	Tavernier *et al.*, 1983
Adenovirus 5 E2	ElA	Imperiale *et al.*, 1984
Collagenase	Phorbol Ester (TPA)	Angel *et al.*, 1987a
Stromelysin	Phorbol Ester (TPA)	Angel *et al.*, 1987b

TABLE 20 Inducible Elements		
Element	Inducer	References
SV40	Phorbol Ester (TPA)	Angel *et al.*, 1987b
Murine MX Gene	Interferon, Newcastle Disease Virus	Hug *et al.*, 1988
GRP78 Gene	A23187	Resendez *et al.*, 1988
α-2-Macroglobulin	IL-6	Kunz *et al.*, 1989
Vimentin	Serum	Rittling *et al.*, 1989
MHC Class I Gene H-2κb	Interferon	Blanar *et al.*, 1989
HSP70	ElA, SV40 Large T Antigen	Taylor *et al.*, 1989, 1990a, 1990b
Proliferin	Phorbol Ester-TPA	Mordacq *et al.*, 1989
Tumor Necrosis Factor α	PMA	Hensel *et al.*, 1989
Thyroid Stimulating Hormone α Gene	Thyroid Hormone	Chatterjee *et al.*, 1989

The identity of tissue-specific promoters or elements, as well as assays to characterize their activity, is well known to those of skill in the art. Non-limiting examples of such regions include the human LIMK2 gene (Nomoto *et al.*, 1999), the somatostatin receptor 2 gene (Kraus *et al.*, 1998), murine epididymal retinoic acid-binding gene (Lareyre *et al.*, 1999), human CD4 (Zhao-Emonet *et al.*, 1998), mouse α2 (XI) collagen (Tsumaki *et al.*, 1998), D1A dopamine receptor gene (Lee *et al.*, 1997), insulin-like growth factor II (Wu *et al.*, 1997), and human platelet endothelial cell adhesion molecule-1 (Almendro *et al.*, 1996). Of particular interest are the neuronal promoter NSE (neuron-specific enolase), and the glial promoter GFAP (glial fibrillary acidic protein).

b. Initiation Signals and Internal Ribosome Binding Sites

A specific initiation signal also may be required for efficient translation of coding sequences. These signals include the ATG initiation codon or adjacent sequences. Exogenous translational control signals, including the ATG initiation codon, may need to be provided. One of ordinary skill in the art would readily be capable of determining this and providing the

necessary signals. It is well known that the initiation codon must be "in-frame" with the reading frame of the desired coding sequence to ensure translation of the entire insert. The exogenous translational control signals and initiation codons can be either natural or synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements.

In certain embodiments of the invention, the use of internal ribosome entry sites (IRES) elements are used to create multigene, or polycistronic, messages. IRES elements are able to bypass the ribosome scanning model of 5′–methylated Cap dependent translation and begin translation at internal sites (Pelletier and Sonenberg, 1988). IRES elements from two members of the picornavirus family (polio and encephalomyocarditis) have been described (Pelletier and Sonenberg, 1988), as well an IRES from a mammalian message (Macejak and Sarnow, 1991). IRES elements can be linked to heterologous open reading frames. Multiple open reading frames can be transcribed together, each separated by an IRES, creating polycistronic messages. By virtue of the IRES element, each open reading frame is accessible to ribosomes for efficient translation. Multiple genes can be efficiently expressed using a single promoter/enhancer to transcribe a single message (see U.S. Patents 5,925,565 and 5,935,819, each herein incorporated by reference).

c. Multiple Cloning Sites

Vectors can include a multiple cloning site (MCS), which is a nucleic acid region that contains multiple restriction enzyme sites, any of which can be used in conjunction with standard recombinant technology to digest the vector (see, for example, Carbonelli *et al.,* 1999, Levenson *et al.,* 1998, and Cocea, 1997, incorporated herein by reference.) "Restriction enzyme digestion" refers to catalytic cleavage of a nucleic acid molecule with an enzyme that functions only at specific locations in a nucleic acid molecule. Many of these restriction enzymes are commercially available. Use of such enzymes is widely understood by those of skill in the art. Frequently, a vector is linearized or fragmented using a restriction enzyme that cuts within the MCS to enable exogenous sequences to be ligated to the vector. "Ligation" refers to the process of forming phosphodiester bonds between two nucleic acid fragments, which may or may not be contiguous with each other. Techniques involving restriction enzymes and ligation reactions are well known to those of skill in the art of recombinant technology.

d. Splicing Sites

Most transcribed eukaryotic RNA molecules will undergo RNA splicing to remove introns from the primary transcripts. Vectors containing genomic eukaryotic sequences may require donor and/or acceptor splicing sites to ensure proper processing of the transcript for protein expression (see, for example, Chandler *et al.*, 1997, herein incorporated by reference).

e. Termination Signals

The vectors or constructs of the present invention will generally comprise at least one termination signal. A "termination signal" or "terminator" is comprised of the DNA sequences involved in specific termination of an RNA transcript by an RNA polymerase. Thus, in certain embodiments a termination signal that ends the production of an RNA transcript is contemplated.

A terminator may be necessary *in vivo* to achieve desirable message levels.

In eukaryotic systems, the terminator region may also comprise specific DNA sequences that permit site-specific cleavage of the new transcript so as to expose a polyadenylation site. This signals a specialized endogenous polymerase to add a stretch of about 200 A residues (polyA) to the 3' end of the transcript. RNA molecules modified with this polyA tail appear to more stable and are translated more efficiently. Thus, in other embodiments involving eukaryotes, it is preferred that that terminator comprises a signal for the cleavage of the RNA, and it is more preferred that the terminator signal promotes polyadenylation of the message. The terminator and/or polyadenylation site elements can serve to enhance message levels and to minimize read through from the cassette into other sequences.

Terminators contemplated for use in the invention include any known terminator of transcription described herein or known to one of ordinary skill in the art, including but not limited to, for example, the termination sequences of genes, such as for example the bovine growth hormone terminator or viral termination sequences, such as for example the SV40 terminator. In certain embodiments, the termination signal may be a lack of transcribable or translatable sequence, such as due to a sequence truncation.

f. Polyadenylation Signals

In expression, particularly eukaryotic expression, one will typically include a polyadenylation signal to effect proper polyadenylation of the transcript. The nature of the polyadenylation signal is not believed to be crucial to the successful practice of the invention, and any such sequence may be employed. Preferred embodiments include the SV40 polyadenylation signal or the bovine growth hormone polyadenylation signal, convenient and known to function well in various target cells. Polyadenylation may increase the stability of the transcript or may facilitate cytoplasmic transport.

g. Origins of Replication

In order to propagate a vector in a host cell, it may contain one or more origins of replication sites (often termed "ori"), which is a specific nucleic acid sequence at which replication is initiated. Alternatively an autonomously replicating sequence (ARS) can be employed if the host cell is yeast.

h. Selectable and Screenable Markers

In certain embodiments of the invention, cells containing a nucleic acid construct of the present invention may be identified *in vitro* or *in vivo* by including a marker in the expression vector. Such markers would confer an identifiable change to the cell permitting easy identification of cells containing the expression vector. Generally, a selectable marker is one that confers a property that allows for selection. A positive selectable marker is one in which the presence of the marker allows for its selection, while a negative selectable marker is one in which its presence prevents its selection. An example of a positive selectable marker is a drug resistance marker.

Usually the inclusion of a drug selection marker aids in the cloning and identification of transformants, for example, genes that confer resistance to neomycin, puromycin, hygromycin, DHFR, GPT, zeocin and histidinol are useful selectable markers. In addition to markers conferring a phenotype that allows for the discrimination of transformants based on the implementation of conditions, other types of markers including screenable markers such as GFP, whose basis is colorimetric analysis, are also contemplated. Alternatively, screenable enzymes such as herpes simplex virus thymidine kinase (*tk*) or chloramphenicol acetyltransferase (CAT)

may be utilized. One of skill in the art would also know how to employ immunologic markers, possibly in conjunction with FACS analysis. The marker used is not believed to be important, so long as it is capable of being expressed simultaneously with the nucleic acid encoding a gene product. Further examples of selectable and screenable markers are well known to one of skill in the art.

i. Plasmid Vectors

In certain embodiments, a plasmid vector is contemplated for use to transform a host cell. In general, plasmid vectors containing replicon and control sequences which are derived from species compatible with the host cell are used in connection with these hosts. The vector ordinarily carries a replication site, as well as marking sequences which are capable of providing phenotypic selection in transformed cells. In a non-limiting example, *E. coli* is often transformed using derivatives of pBR322, a plasmid derived from an *E. coli* species. pBR322 contains genes for ampicillin and tetracycline resistance and thus provides easy means for identifying transformed cells. The pBR plasmid, or other microbial plasmid or phage must also contain, or be modified to contain, for example, promoters which can be used by the microbial organism for expression of its own proteins.

In addition, phage vectors containing replicon and control sequences that are compatible with the host microorganism can be used as transforming vectors in connection with these hosts. For example, the phage lambda GEM^{TM}-11 may be utilized in making a recombinant phage vector which can be used to transform host cells, such as, for example, *E. coli* LE392. Further useful plasmid vectors include pIN vectors (Inouye *et al.*, 1985); and pGEX vectors, for use in generating glutathione S-transferase (GST) soluble fusion proteins for later purification and separation or cleavage. Other suitable fusion proteins are those with β-galactosidase, ubiquitin, and the like.

Bacterial host cells, for example, *E. coli*, comprising the expression vector, are grown in any of a number of suitable media, for example, LB. The expression of the recombinant protein in certain vectors may be induced, as would be understood by those of skill in the art, by contacting a host cell with an agent specific for certain promoters, *e.g.*, by adding IPTG to the media or by switching incubation to a higher temperature. After culturing the bacteria for a

further period, generally of between 2 and 24 h, the cells are collected by centrifugation and washed to remove residual media.

j. Viral Vectors

The ability of certain viruses to infect cells or enter cells *via* receptor-mediated endocytosis, and to integrate into host cell genome and express viral genes stably and efficiently have made them attractive candidates for the transfer of foreign nucleic acids into cells (*e.g.*, mammalian cells). Non-limiting examples of virus vectors that may be used to deliver a nucleic acid of the present invention are described below.

1. Adenoviral Vectors

A particular method for delivery of the nucleic acid involves the use of an adenovirus expression vector. Although adenovirus vectors are known to have a low capacity for integration into genomic DNA, this feature is counterbalanced by the high efficiency of gene transfer afforded by these vectors. "Adenovirus expression vector" is meant to include those constructs containing adenovirus sequences sufficient to (a) support packaging of the construct and (b) to ultimately express a tissue or cell-specific construct that has been cloned therein. Knowledge of the genetic organization or adenovirus, a 36 kb, linear, double-stranded DNA virus, allows substitution of large pieces of adenoviral DNA with foreign sequences up to 7 kb (Grunhaus and Horwitz, 1992).

2. AAV Vectors

The nucleic acid may be introduced into the cell using adenovirus assisted transfection. Increased transfection efficiencies have been reported in cell systems using adenovirus coupled systems (Kelleher and Vos, 1994; Cotten *et al.*, 1992; Curiel, 1994). Adeno-associated virus (AAV) is an attractive vector system as it has a high frequency of integration and it can infect non-dividing cells, thus making it useful for delivery of genes into mammalian cells, for example, in tissue culture (Muzyczka, 1992) or *in vivo*. AAV has a broad host range for infectivity (Tratschin *et al.*, 1984; Laughlin *et al.*, 1986; Lebkowski *et al.*, 1988; McLaughlin *et al.*, 1988). Details concerning the generation and use of rAAV vectors are described in U.S. Patents 5,139,941 and 4,797,368, each incorporated herein by reference.

3. Retroviral Vectors

Retroviruses have promise as gene delivery vectors due to their ability to integrate their genes into the host genome, transferring a large amount of foreign genetic material, infecting a broad spectrum of species and cell types and of being packaged in special cell-lines (Miller, 1992).

In order to construct a retroviral vector, a nucleic acid (*e.g.*, one encoding gene of interest) is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. In order to produce virions, a packaging cell line containing the gag, pol, and env genes but without the LTR and packaging components is constructed (Mann *et al.*, 1983). When a recombinant plasmid containing a cDNA, together with the retroviral LTR and packaging sequences is introduced into a special cell line (*e.g.*, by calcium phosphate precipitation for example), the packaging sequence allows the RNA transcript of the recombinant plasmid to be packaged into viral particles, which are then secreted into the culture media (Nicolas and Rubenstein, 1988; Temin, 1986; Mann *et al.*, 1983). The media containing the recombinant retroviruses is then collected, optionally concentrated, and used for gene transfer. Retroviral vectors are able to infect a broad variety of cell types. However, integration and stable expression require the division of host cells (Paskind *et al.*, 1975).

Lentiviruses are complex retroviruses, which, in addition to the common retroviral genes *gag, pol*, and *env*, contain other genes with regulatory or structural function. Lentiviral vectors are well known in the art (see, for example, Naldini *et al.*, 1996; Zufferey *et al.*, 1997; Blomer *et al.*, 1997; U.S. Patents 6,013,516 and 5,994,136). Some examples of lentivirus include the Human Immunodeficiency Viruses: HIV-1, HIV-2 and the Simian Immunodeficiency Virus: SIV. Lentiviral vectors have been generated by multiply attenuating the HIV virulence genes, for example, the genes *env, vif, vpr, vpu* and *nef* are deleted making the vector biologically safe. Recombinant lentiviral vectors are capable of infecting non-dividing cells and can be used for both *in vivo* and *ex vivo* gene transfer and expression of nucleic acid sequences. For example, recombinant lentivirus capable of infecting a non-dividing cell wherein a suitable host cell is transfected with two or more vectors carrying the packaging functions, namely gag, pol and env, as well as rev and tat is described in U.S. Patent 5,994,136, incorporated herein by reference. One may target the recombinant virus by linkage of the envelope protein with an antibody or a

particular ligand for targeting to a receptor of a particular cell-type. By inserting a sequence (including a regulatory region) of interest into the viral vector, along with another gene which encodes the ligand for a receptor on a specific target cell, for example, the vector is now target-specific.

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4. Other Viral Vectors

Other viral vectors may be employed as vaccine constructs in the present invention. Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988; Baichwal and Sugden, 1986; Coupar *et al.,* 1988), sindbis virus, cytomegalovirus and herpes simplex virus may be 10 employed. They offer several attractive features for various mammalian cells (Friedmann, 1989; Ridgeway, 1988; Baichwal and Sugden, 1986; Coupar *et al.,* 1988; Horwich *et al.,* 1990).

5. Delivery Using Modified Viruses

A nucleic acid to be delivered may be housed within an infective virus that has been 15 engineered to express a specific binding ligand. The virus particle will thus bind specifically to the cognate receptors of the target cell and deliver the contents to the cell. A novel approach designed to allow specific targeting of retrovirus vectors was developed based on the chemical modification of a retrovirus by the chemical addition of lactose residues to the viral envelope. This modification can permit the specific infection of hepatocytes *via* sialoglycoprotein 20 receptors.

Another approach to targeting of recombinant retroviruses was designed in which biotinylated antibodies against a retroviral envelope protein and against a specific cell receptor were used. The antibodies were coupled *via* the biotin components by using streptavidin (Roux *et al.,* 1989). Using antibodies against major histocompatibility complex class I and class 25 II antigens, they demonstrated the infection of a variety of human cells that bore those surface antigens with an ecotropic virus *in vitro* (Roux *et al.,* 1989).

7. Vector Delivery and Cell Transformation

Suitable methods for nucleic acid delivery for transformation of an organelle, a cell, a 30 tissue or an organism for use with the current invention are believed to include virtually any method by which a nucleic acid (*e.g.*, DNA) can be introduced into an organelle, a cell, a tissue

or an organism, as described herein or as would be known to one of ordinary skill in the art. Such methods include, but are not limited to, direct delivery of DNA such as by *ex vivo* transfection (Wilson *et al.*, 1989, Nabel and Baltimore, 1987), by injection (U.S. Patents 5,994,624, 5,981,274, 5,945,100, 5,780,448, 5,736,524, 5,702,932, 5,656,610, 5,589,466 and 5,580,859, each incorporated herein by reference), including microinjection (Harlan and Weintraub, 1985; U.S. Patent 5,789,215, incorporated herein by reference); by electroporation (U.S. Patent 5,384,253, incorporated herein by reference; Tur-Kaspa *et al.*, 1986; Potter *et al.*, 1984); by calcium phosphate precipitation (Graham and Van Der Eb, 1973; Chen and Okayama, 1987; Rippe *et al.*, 1990); by using DEAE-dextran followed by polyethylene glycol (Gopal, 1985); by direct sonic loading (Fechheimer *et al.*, 1987); by liposome mediated transfection (Nicolau and Sene, 1982; Fraley *et al.*, 1979; Nicolau *et al.*, 1987; Wong *et al.*, 1980; Kaneda *et al.*, 1989; Kato *et al.*, 1991) and receptor-mediated transfection (Wu and Wu, 1987; Wu and Wu, 1988); by microprojectile bombardment (PCT Application Nos. WO 94/09699 and 95/06128; U.S. Patents 5,610,042; 5,322,783 5,563,055, 5,550,318, 5,538,877 and 5,538,880, and each incorporated herein by reference); by agitation with silicon carbide fibers (Kaeppler *et al.*, 1990; U.S. Patents 5,302,523 and 5,464,765, each incorporated herein by reference); by PEG-mediated transformation of protoplasts (Omirulleh *et al.*, 1993; U.S. Patents 4,684,611 and 4,952,500, each incorporated herein by reference); by desiccation/inhibition-mediated DNA uptake (Potrykus *et al.*, 1985), and any combination of such methods. Through the application of techniques such as these, organelle(s), cell(s), tissue(s) or organism(s) may be stably or transiently transformed.

a. Injection

In certain embodiments, a nucleic acid may be delivered to an organelle, a cell, a tissue or an organism via one or more injections (*i.e.*, a needle injection), such as, for example, subcutaneously, intradermally, intramuscularly, intervenously, intraperitoneally, *etc.* Methods of injection of vaccines are well known to those of ordinary skill in the art (*e.g.*, injection of a composition comprising a saline solution). Further embodiments of the present invention include the introduction of a nucleic acid by direct microinjection. Direct microinjection has been used to introduce nucleic acid constructs into *Xenopus* oocytes (Harland and Weintraub, 1985).

b. Electroporation

In certain embodiments of the present invention, a nucleic acid is introduced into an organelle, a cell, a tissue or an organism *via* electroporation. Electroporation involves the exposure of a suspension of cells and DNA to a high-voltage electric discharge. In some variants of this method, certain cell wall-degrading enzymes, such as pectin-degrading enzymes, are employed to render the target recipient cells more susceptible to transformation by electroporation than untreated cells (U.S. Patent 5,384,253, incorporated herein by reference). Alternatively, recipient cells can be made more susceptible to transformation by mechanical wounding.

Transfection of eukaryotic cells using electroporation has been quite successful. Mouse pre-B lymphocytes have been transfected with human kappa-immunoglobulin genes (Potter *et al.,* 1984), and rat hepatocytes have been transfected with the chloramphenicol acetyltransferase gene (Tur-Kaspa *et al.,* 1986) in this manner.

c. Calcium Phosphate

In other embodiments of the present invention, a nucleic acid may be introduced to the cells using calcium phosphate precipitation in an *ex vivo* context. Human KB cells have been transfected with adenovirus 5 DNA (Graham and Van Der Eb, 1973) using this technique. Also in this manner, mouse L(A9), mouse C127, CHO, CV-1, BHK, NIH3T3 and HeLa cells were transfected with a neomycin marker gene (Chen and Okayama, 1987), and rat hepatocytes were transfected with a variety of marker genes (Rippe *et al.,* 1990).

d. DEAE-Dextran

In another embodiment, a nucleic acid is delivered into a cell using DEAE-dextran followed by polyethylene glycol. In this manner, reporter plasmids were introduced into mouse myeloma and erythroleukemia cells (Gopal, 1985).

e. Sonication Loading

Additional embodiments of the present invention include the introduction of a nucleic acid by direct sonic loading. LTK$^-$ fibroblasts have been transfected with the thymidine kinase gene by sonication loading (Fechheimer *et al.*, 1987).

f. Liposome-Mediated Transfection

In a further embodiment of the invention, a nucleic acid may be entrapped in a lipid complex such as, for example, a liposome. Liposomes are vesicular structures characterized by a phospholipid bilayer membrane and an inner aqueous medium. Multilamellar liposomes have multiple lipid layers separated by aqueous medium. They form spontaneously when phospholipids are suspended in an excess of aqueous solution. The lipid components undergo self-rearrangement before the formation of closed structures and entrap water and dissolved solutes between the lipid bilayers (Ghosh and Bachhawat, 1991). Also contemplated is a nucleic acid complexed with Lipofectamine (Gibco BRL) or Superfect (Qiagen).

Liposome-mediated nucleic acid delivery and expression of foreign DNA *in vitro* has been very successful (Nicolau and Sene, 1982; Fraley *et al.*, 1979; Nicolau *et al.*, 1987). The feasibility of liposome-mediated delivery and expression of foreign DNA in cultured chick embryo, HeLa and hepatoma cells has also been demonstrated (Wong *et al.*, 1980).

In certain embodiments of the invention, a liposome may be complexed with a hemagglutinating virus (HVJ). This has been shown to facilitate fusion with the cell membrane and promote cell entry of liposome-encapsulated DNA (Kaneda *et al.*, 1989). In other embodiments, a liposome may be complexed or employed in conjunction with nuclear non-histone chromosomal proteins (HMG-1) (Kato *et al.*, 1991). In yet further embodiments, a liposome may be complexed or employed in conjunction with both HVJ and HMG-1. In other embodiments, a delivery vehicle may comprise a ligand and a liposome.

g. Receptor Mediated Transfection

Still further, a nucleic acid may be delivered to a target cell via receptor-mediated delivery vehicles. These take advantage of the selective uptake of macromolecules by receptor-mediated endocytosis that will be occurring in a target cell. In view of the cell

type-specific distribution of various receptors, this delivery method adds another degree of specificity to the present invention.

Certain receptor-mediated gene targeting vehicles comprise a cell receptor-specific ligand and a nucleic acid-binding agent. Others comprise a cell receptor-specific ligand to which the nucleic acid to be delivered has been operatively attached. Several ligands have been used for receptor-mediated gene transfer (Wu and Wu, 1987; Wagner *et al.*, 1990; Perales *et al.*, 1994; Myers, EPO 0273085), which establishes the operability of the technique. Specific delivery in the context of another mammalian cell type has been described (Wu and Wu, 1993; incorporated herein by reference). In certain aspects of the present invention, a ligand will be chosen to correspond to a receptor specifically expressed on the target cell population.

In other embodiments, a nucleic acid delivery vehicle component of a cell-specific nucleic acid targeting vehicle may comprise a specific binding ligand in combination with a liposome. The nucleic acid(s) to be delivered are housed within the liposome and the specific binding ligand is functionally incorporated into the liposome membrane. The liposome will thus specifically bind to the receptor(s) of a target cell and deliver the contents to a cell. Such systems have been shown to be functional using systems in which, for example, epidermal growth factor (EGF) is used in the receptor-mediated delivery of a nucleic acid to cells that exhibit upregulation of the EGF receptor.

In still further embodiments, the nucleic acid delivery vehicle component of a targeted delivery vehicle may be a liposome itself, which will preferably comprise one or more lipids or glycoproteins that direct cell-specific binding. For example, lactosyl-ceramide, a galactose-terminal asialganglioside, has been incorporated into liposomes and an increase in the uptake of the insulin gene by hepatocytes has been observed (Nicolau *et al.*, 1987). It is contemplated that the tissue-specific transforming constructs of the present invention can be specifically delivered into a target cell in a similar manner.

h. Microprojectile Bombardment

Microprojectile bombardment techniques can be used to introduce a nucleic acid *ex vivo* into at least one, organelle, cell, or tissue (U.S. Patents 5,550,318, 5,538,880, 5,610,042, and PCT Application WO 94/09699; each of which is incorporated herein by reference). This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity

allowing them to pierce cell membranes and enter cells without killing them (Klein *et al.*, 1987). There are a wide variety of microprojectile bombardment techniques known in the art, many of which are applicable to the invention.

In this microprojectile bombardment, one or more particles may be coated with at least one nucleic acid and delivered into cells by a propelling force. Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang *et al.*, 1990). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold particles or beads. Exemplary particles include those comprised of tungsten, platinum, and preferably, gold. It is contemplated that in some instances DNA precipitation onto metal particles would not be necessary for DNA delivery to a recipient cell using microprojectile bombardment. However, it is contemplated that particles may contain DNA rather than be coated with DNA. DNA-coated particles may increase the level of DNA delivery via particle bombardment but are not, in and of themselves, necessary.

IV. Methods of Assaying for Alterations in Gene Expression

In accordance with the present invention, methods are provided for assessing the ability of a genetic construct to alter the expression of target genes in patients suffering from or at risk of MS. In each of these assays, the expression of one or more genes, identified in Tables 1-15, will be measured. Genes that play a role in the immune system can be targeted to, and measured from the peripheral blood cells, or alternatively, targeted to, and measured directly from, the inflammatory lesions (*i.e.*, when lesions are biopsied to rule out tumors). Non-immune genes (for instance, genes associated with neurodegeneration or demyelination) can be targeted to, and measured from (if biopsy is done), the brain or spinal cord lesions, regardless of the presence or absence of inflammation. The following is a discussion of various aspects of these methods.

1. Hybridization

There are a variety of ways by which one can assess gene expression. These methods either look at protein or at mRNA levels. Methods looking at mRNAs all fundamentally rely, at a basic level, on nucleic acid hybridization. Hybridization is defined as the ability of a nucleic acid to selectively form duplex molecules with complementary stretches of DNAs and/or RNAs.

Depending on the application envisioned, one would employ varying conditions of hybridization to achieve varying degrees of selectivity of the probe or primers for the target sequence.

Typically, a probe or primer of between 13 and 100 nucleotides, preferably between 17 and 100 nucleotides in length up to 1-2 kilobases or more in length will allow the formation of a duplex molecule that is both stable and selective. Molecules having complementary sequences over contiguous stretches greater than 20 bases in length are generally preferred, to increase stability and selectivity of the hybrid molecules obtained. One will generally prefer to design nucleic acid molecules for hybridization having one or more complementary sequences of 20 to 30 nucleotides, or even longer where desired. Such fragments may be readily prepared, for example, by directly synthesizing the fragment by chemical means or by introducing selected sequences into recombinant vectors for recombinant production.

For applications requiring high selectivity, one will typically desire to employ relatively high stringency conditions to form the hybrids. For example, relatively low salt and/or high temperature conditions, such as provided by about 0.02 M to about 0.10 M NaCl at temperatures of about 50°C to about 70°C. Such high stringency conditions tolerate little, if any, mismatch between the probe or primers and the template or target strand and would be particularly suitable for isolating specific genes or for detecting specific mRNA transcripts. It is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide.

For certain applications, for example, lower stringency conditions may be used. Under these conditions, hybridization may occur even though the sequences of the hybridizing strands are not perfectly complementary, but are mismatched at one or more positions. Conditions may be rendered less stringent by increasing salt concentration and/or decreasing temperature. For example, a medium stringency condition could be provided by about 0.1 to 0.25 M NaCl at temperatures of about 37°C to about 55°C, while a low stringency condition could be provided by about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Hybridization conditions can be readily manipulated depending on the desired results.

In other embodiments, hybridization may be achieved under conditions of, for example, 50 mM Tris-HCl (pH 8.3), 75 mM KCl, 3 mM $MgCl_2$, 1.0 mM dithiothreitol, at temperatures between approximately 20°C to about 37°C. Other hybridization conditions utilized could include approximately 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, at temperatures ranging from approximately 40°C to about 72°C.

In certain embodiments, it will be advantageous to employ nucleic acids of defined sequences of the present invention in combination with an appropriate means, such as a label, for determining hybridization. A wide variety of appropriate indicator means are known in the art, including fluorescent, radioactive, enzymatic or other ligands, such as avidin/biotin, which are capable of being detected. In preferred embodiments, one may desire to employ a fluorescent label or an enzyme tag such as urease, alkaline phosphatase or peroxidase, instead of radioactive or other environmentally undesirable reagents. In the case of enzyme tags, colorimetric indicator substrates are known that can be employed to provide a detection means that is visibly or spectrophotometrically detectable, to identify specific hybridization with complementary nucleic acid containing samples.

In general, it is envisioned that the probes or primers described herein will be useful as reagents in solution hybridization, as in PCR™, for detection of expression of corresponding genes, as well as in embodiments employing a solid phase. In embodiments involving a solid phase, the test DNA (or RNA) is adsorbed or otherwise affixed to a selected matrix or surface. This fixed, single-stranded nucleic acid is then subjected to hybridization with selected probes under desired conditions. The conditions selected will depend on the particular circumstances (depending, for example, on the G+C content, type of target nucleic acid, source of nucleic acid, size of hybridization probe, *etc.*). Optimization of hybridization conditions for the particular application of interest is well known to those of skill in the art. After washing of the hybridized molecules to remove non-specifically bound probe molecules, hybridization is detected, and/or quantified, by determining the amount of bound label. Representative solid phase hybridization methods are disclosed in U.S. Patents 5,843,663, 5,900,481 and 5,919,626. Other methods of hybridization that may be used in the practice of the present invention are disclosed in U.S. Patents 5,849,481, 5,849,486 and 5,851,772. The relevant portions of these and other references identified in this section of the Specification are incorporated herein by reference.

2. Amplification of Nucleic Acids

Since many nucleic acids, especially mRNAs, are in low abundance, nucleic acid amplification greatly enhances the ability to assess expression. The general concept is that nucleic acids can be amplified using paired primers flanking the region of interest. The term "primer," as used herein, is meant to encompass any nucleic acid that is capable of priming the

synthesis of a nascent nucleic acid in a template-dependent process. Typically, primers are oligonucleotides from ten to twenty and/or thirty base pairs in length, but longer sequences can be employed. Primers may be provided in double-stranded and/or single-stranded form, although the single-stranded form is preferred.

Pairs of primers designed to selectively hybridize to nucleic acids corresponding to selected genes are contacted with the template nucleic acid under conditions that permit selective hybridization. Depending upon the desired application, high stringency hybridization conditions may be selected that will only allow hybridization to sequences that are completely complementary to the primers. In other embodiments, hybridization may occur under reduced stringency to allow for amplification of nucleic acids containing one or more mismatches with the primer sequences. Once hybridized, the template-primer complex is contacted with one or more enzymes that facilitate template-dependent nucleic acid synthesis. Multiple rounds of amplification, also referred to as "cycles," are conducted until a sufficient amount of amplification product is produced.

The amplification product may be detected or quantified. In certain applications, the detection may be performed by visual means. Alternatively, the detection may involve indirect identification of the product via chemilluminescence, radioactive scintigraphy of incorporated radiolabel or fluorescent label or even via a system using electrical and/or thermal impulse signals.

A number of template dependent processes are available to amplify the oligonucleotide sequences present in a given template sample. One of the best known amplification methods is the polymerase chain reaction (referred to as PCR™) which is described in detail in U.S. Patents 4,683,195, 4,683,202 and 4,800,159, and in Innis *et al.*, 1988, each of which is incorporated herein by reference in their entirety.

A reverse transcriptase PCR™ amplification procedure may be performed to quantify the amount of mRNA amplified. Methods of reverse transcribing RNA into cDNA are well known (see Sambrook *et al.*, 1989). Alternative methods for reverse transcription utilize thermostable DNA polymerases. These methods are described in WO 90/07641. Polymerase chain reaction methodologies are well known in the art. Representative methods of RT-PCR are described in U.S. Patent 5,882,864.

Whereas standard PCR usually uses one pair of primers to amplify a specific sequence, multiplex-PCR (MPCR) uses multiple pairs of primers to amplify many sequences simultaneously (Chamberlan *et al.*, 1990). The presence of many PCR primers in a single tube could cause many problems, such as the increased formation of misprimed PCR products and "primer dimers," the amplification discrimination of longer DNA fragment and so on. Normally, MPCR buffers contain a Taq Polymerase additive, which decreases the competition among amplicons and the amplification discrimination of longer DNA fragment during MPCR. MPCR products can further be hybridized with gene-specific probe for verification. Theoretically, one should be able to use as many as primers as necessary. However, due to side effects (primer dimers, misprimed PCR products, *etc.*) caused during MPCR, there is a limit (less than 20) to the number of primers that can be used in a MPCR reaction. See also European Application No. 0 364 255 and Mueller & Wold (1989).

Another method for amplification is ligase chain reaction ("LCR"), disclosed in European Application No. 320 308, incorporated herein by reference in its entirety. U.S. Patent 4,883,750 describes a method similar to LCR for binding probe pairs to a target sequence. A method based on PCR™ and oligonucleotide ligase assay (OLA), disclosed in U.S. Patent 5,912,148, may also be used.

Alternative methods for amplification of target nucleic acid sequences that may be used in the practice of the present invention are disclosed in U.S. Patents 5,843,650, 5,846,709, 5,846,783, 5,849,546, 5,849,497, 5,849,547, 5,858,652, 5,866,366, 5,916,776, 5,922,574, 5,928,905, 5,928,906, 5,932,451, 5,935,825, 5,939,291 and 5,942,391, GB Application No. 2 202 328, and in PCT Application No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety.

Qbeta Replicase, described in PCT Application No. PCT/US87/00880, may also be used as an amplification method in the present invention. In this method, a replicative sequence of RNA that has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence which may then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5'-[α-thio]-triphosphates in one strand of a restriction site may also be useful in the amplification of nucleic acids in the present invention (Walker *et al.*, 1992). Strand Displacement Amplification (SDA), disclosed in U.S.

Patent 5,916,779, is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, *i.e.*, nick translation.

Other nucleic acid amplification procedures include transcription-based amplification systems (TAS), including nucleic acid sequence based amplification (NASBA) and 3SR (Kwoh *et al.*, 1989; Gingeras *et al.*, PCT Application WO 88/10315, incorporated herein by reference in their entirety). European Application No. 329 822 disclose a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA), which may be used in accordance with the present invention.

PCT Application WO 89/06700 (incorporated herein by reference in its entirety) disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter region/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. This scheme is not cyclic, *i.e.*, new templates are not produced from the resultant RNA transcripts. Other amplification methods include "race" and "one-sided PCR" (Frohman, 1990; Ohara *et al.*, 1989).

3. Detection of Nucleic Acids

Following any amplification, it may be desirable to separate the amplification product from the template and/or the excess primer. In one embodiment, amplification products are separated by agarose, agarose-acrylamide or polyacrylamide gel electrophoresis using standard methods (Sambrook *et al.*, 1989). Separated amplification products may be cut out and eluted from the gel for further manipulation. Using low melting point agarose gels, the separated band may be removed by heating the gel, followed by extraction of the nucleic acid.

Separation of nucleic acids may also be effected by chromatographic techniques known in art. There are many kinds of chromatography which may be used in the practice of the present invention, including adsorption, partition, ion-exchange, hydroxylapatite, molecular sieve, reverse-phase, column, paper, thin-layer, and gas chromatography as well as HPLC.

In certain embodiments, the amplification products are visualized. A typical visualization method involves staining of a gel with ethidium bromide and visualization of bands under UV light. Alternatively, if the amplification products are integrally labeled with radio- or fluorometrically-labeled nucleotides, the separated amplification products can be exposed to x-ray film or visualized under the appropriate excitatory spectra.

In one embodiment, following separation of amplification products, a labeled nucleic acid probe is brought into contact with the amplified marker sequence. The probe preferably is conjugated to a chromophore but may be radiolabeled. In another embodiment, the probe is conjugated to a binding partner, such as an antibody or biotin, or another binding partner carrying a detectable moiety.

In particular embodiments, detection is by Southern blotting and hybridization with a labeled probe. The techniques involved in Southern blotting are well known to those of skill in the art (see Sambrook *et al.*, 1989). One example of the foregoing is described in U.S. Patent 5,279,721, incorporated by reference herein, which discloses an apparatus and method for the automated electrophoresis and transfer of nucleic acids. The apparatus permits electrophoresis and blotting without external manipulation of the gel and is ideally suited to carrying out methods according to the present invention.

Other methods of nucleic acid detection that may be used in the practice of the instant invention are disclosed in U.S. Patents 5,840,873, 5,843,640, 5,843,651, 5,846,708, 5,846,717, 5,846,726, 5,846,729, 5,849,487, 5,853,990, 5,853,992, 5,853,993, 5,856,092, 5,861,244, 5,863,732, 5,863,753, 5,866,331, 5,905,024, 5,910,407, 5,912,124, 5,912,145, 5,919,630, 5,925,517, 5,928,862, 5,928,869, 5,929,227, 5,932,413 and 5,935,791, each of which is incorporated herein by reference.

4. Nucleic Acid Arrays

Microarrays comprise a plurality of polymeric molecules spatially distributed over, and stably associated with, the surface of a substantially planar substrate, *e.g.*, biochips. Microarrays of polynucleotides have been developed and find use in a variety of applications, such as screening and DNA sequencing. One area in particular in which microarrays find use is in gene expression analysis.

In gene expression analysis with microarrays, an array of "probe" oligonucleotides is contacted with a nucleic acid sample of interest, *i.e.*, target, such as polyA mRNA or total RNA from a particular tissue type. Contact is carried out under hybridization conditions and unbound nucleic acid is then removed. The resultant pattern of hybridized nucleic acid provides information regarding the genetic profile of the sample tested. Methodologies of gene

expression analysis on microarrays are capable of providing both qualitative and quantitative information.

A variety of different arrays which may be used are known in the art. The probe molecules of the arrays which are capable of sequence specific hybridization with target nucleic acid may be polynucleotides or hybridizing analogues or mimetics thereof, including: nucleic acids in which the phosphodiester linkage has been replaced with a substitute linkage, such as phophorothioate, methylimino, methylphosphonate, phosphoramidate, guanidine and the like; nucleic acids in which the ribose subunit has been substituted, *e.g.*, hexose phosphodiester; peptide nucleic acids; and the like. The length of the probes will generally range from 10 to 1000 nts, where in some embodiments the probes will be oligonucleotides and usually range from 15 to 150 nts and more usually from 15 to 100 nts in length, and in other embodiments the probes will be longer, usually ranging in length from 150 to 1000 nts, where the polynucleotide probes may be single- or double-stranded, usually single-stranded, and may be PCR fragments amplified from cDNA.

The probe molecules on the surface of the substrates will correspond to selected genes being analyzed and be positioned on the array at a known location so that positive hybridization events may be correlated to expression of a particular gene in the physiological source from which the target nucleic acid sample is derived. The substrates with which the probe molecules are stably associated may be fabricated from a variety of materials, including plastics, ceramics, metals, gels, membranes, glasses, and the like. The arrays may be produced according to any convenient methodology, such as preforming the probes and then stably associating them with the surface of the support or growing the probes directly on the support. A number of different array configurations and methods for their production are known to those of skill in the art and disclosed in U.S. Patents 5,445,934, 5,532,128, 5,556,752, 5,242,974, 5,384,261, 5,405,783, 5,412,087, 5,424,186, 5,429,807, 5,436,327, 5,472,672, 5,527,681, 5,529,756, 5,545,531, 5,554,501, 5,561,071, 5,571,639, 5,593,839, 5,599,695, 5,624,711, 5,658,734, 5,700,637, and 6,004,755.

Following hybridization, where non-hybridized labeled nucleic acid is capable of emitting a signal during the detection step, a washing step is employed where unhybridized labeled nucleic acid is removed from the support surface, generating a pattern of hybridized

nucleic acid on the substrate surface. A variety of wash solutions and protocols for their use are known to those of skill in the art and may be used.

Where the label on the target nucleic acid is not directly detectable, one then contacts the array, now comprising bound target, with the other member(s) of the signal producing system that is being employed. For example, where the label on the target is biotin, one then contacts the array with streptavidin-fluorescer conjugate under conditions sufficient for binding between the specific binding member pairs to occur. Following contact, any unbound members of the signal producing system will then be removed, *e.g.*, by washing. The specific wash conditions employed will necessarily depend on the specific nature of the signal producing system that is employed, and will be known to those of skill in the art familiar with the particular signal producing system employed.

The resultant hybridization pattern(s) of labeled nucleic acids may be visualized or detected in a variety of ways, with the particular manner of detection being chosen based on the particular label of the nucleic acid, where representative detection means include scintillation counting, autoradiography, fluorescence measurement, calorimetric measurement, light emission measurement and the like.

Prior to detection or visualization, where one desires to reduce the potential for a mismatch hybridization event to generate a false positive signal on the pattern, the array of hybridized target/probe complexes may be treated with an endonuclease under conditions sufficient such that the endonuclease degrades single stranded, but not double stranded DNA. A variety of different endonucleases are known and may be used, where such nucleases include: mung bean nuclease, S1 nuclease, and the like. Where such treatment is employed in an assay in which the target nucleic acids are not labeled with a directly detectable label, *e.g.*, in an assay with biotinylated target nucleic acids, the endonuclease treatment will generally be performed prior to contact of the array with the other member(s) of the signal producing system, *e.g.*, fluorescent-streptavidin conjugate. Endonuclease treatment, as described above, ensures that only end-labeled target/probe complexes having a substantially complete hybridization at the 3' end of the probe are detected in the hybridization pattern.

Following hybridization and any washing step(s) and/or subsequent treatments, as described above, the resultant hybridization pattern is detected. In detecting or visualizing the hybridization pattern, the intensity or signal value of the label will be not only detected but

quantified, by which is meant that the measured signal from each hybridization spot is compared to a unit value from the signal emitted by a known number of end-labeled target nucleic acids to obtain an absolute count of the copy number.

V. Pharmaceutical Formulations and Routes of Administration

It will be necessary to prepare pharmaceutical compositions in a form appropriate for use *in vivo*. Generally, this will entail preparing gene therapy vectors that are essentially free of pyrogens, as well as other impurities that could be harmful to humans or animals.

The phrase "pharmaceutically or pharmacologically acceptable" refers to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Supplementary active ingredients also can be incorporated into the compositions.

Administration of these compositions according to the present invention will be *via* any common route so long as the target tissue is available *via* that route. This includes intradermal, subcutaneous, intramuscular, intraperitoneal or intravenous injection. Such compositions would normally be administered as pharmaceutically acceptable compositions, described *supra*.

The active compounds also may be administered intranasally, intraalveolarly (inhaled), parenterally, intrathecally (into the spinal fluid compartment), intraparenchymally (into the brain or spinal cord tissues) or intraperitoneally. Solutions of the active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy administration by a syringe is possible. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as

bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial an antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

For oral administration the polypeptides of the present invention may be incorporated with excipients that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The compositions of the present invention may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example,

hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

VI. Examples

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1 – MATERIALS AND METHODS

RNA isolation and hybridization. All samples were obtained from local or national tissue banks and were processed under full compliance with institutional IRB requirements. Recorded tissue collection times ranged from 2-15 hours post-mortem, with the averages being 4 hours for MS and 10 hours for normals. For DNA microarray analysis, total RNA was obtained from postmortem gray or white matter of lumbar spinal cord from 9 individuals (5 with MS, and 4 controls without neurologic disease, of which 2 white matter control samples yielded sufficient RNA for the study). To assess the gene expression profile of post-mortem MS spinal cords, the inventors compared 4 MS gray matter tissues to 4 gray matter controls and 5 MS white mater tissues to 2 white matter controls (Table 1).

Analysis of the MS spinal cord samples by histopathology of both gray and white matter (average autolysis time 3.2 h), using Luxol Fast Blue, Bodian, H&E stains and GFAP, lymphocyte common antigen (LCA) and CD68 immunostaining revealed sample heterogeneity with findings that ranged from little involvement to frank inflammation, demyelination, or axonal loss. The inventors isolated RNA directly from frozen spinal cord specimens using the Qiagen RNAeasy™ kit, following the manufacturer's recommendations. Briefly, frozen tissues

were dissected to separate gray and white matter, followed by mortar fragmentation in the presence of liquid nitrogen. Total RNA was isolated using the Qiagen Rneasy™ kit with the modification that the upper lipid layer was entirely removed from all samples after resuspension and spinning with buffer RLT. Although this strategy led to the discard of approximately 20-40% of the RNA sample, it preserved the overall integrity of our RNA because the lipid layer is known to compromise RNA stability and quality. All RNA samples included met quality/control standards (*i.e.*, 260/280 OD ratios > 1.8 in all RNA samples, and ratio of 3' to 5' signal > 1.7 for GAPDH and β-actin on GeneChip for RNA samples used in microarray experiments) and were used for microarray hybridization. Though it is recognized that post-mortem changes in levels of individual mRNAs presumably occurred, these were likely similar among the specimens.

The inventors then performed microarray hybridization using RNAs isolated from gray and white matter from these spinal cords, using Affymetrix protocols. DNA microarray analysis was performed using Affymetrix HuFL GeneChip probe arrays. These microarrays contain 7,070 distinct probe sets, representing approximately 6,800 human genes. Briefly, using 7-10 μg of total RNA, double-stranded cDNA was synthesized using the Superscript Choice System (Life Technologies) with the following modifications. In the first strand synthesis, the reverse transcription reaction contained a T7-$(dT)_{24}$ primer plus 0.1 M DTT and 10 mM dNTP mix. For second strand synthesis, *E. coli* DNA ligase (10 U/μl) and T4 DNA Polymerase I (10 U/μl), 10 mM dNTP mix and RNase H (2 U/μl) were used. Phenol-chloroform extraction was followed by *in vitro* transcription (IVT) (Ambion T7 Megascript System) with biotin labeling. IVT was performed with (1:3) biotinylated: unlabeled CTP and UTP. The Ambion T7 enzyme mix and T7 transcription buffer were added to the ds cDNA and NTP labeling mix (ATP, CTP, UTP, GTP, Bio-11-CTP and Bio-16-UTP). The NTP labeling mix was incubated for 5 hr at 37°C, and cleaned using RNeasy columns (Qiagen). Thirteen to 20 μg of fluorescently-labeled and chemically-fragmented cRNA were used for array hybridization. Fragmented cRNA and herring sperm DNA were added to the hybridization buffer containing 1.0 M NaCl, 10 mM Tris-HCL pH 7.6, and 0.01% Triton X-100.

The hybridization mixture was heated to 99°C for 5 min., spun, and incubated at 45°C for 5 min, and injected into the probe array cartridge. Hybridizations were carried out at 45°C for 16 hours with mixing at 60 rpm. Following hybridization, solutions were removed, and arrays were rinsed and incubated with 0.1X ST-T (100 mM NaCl, 10 mM Tris-HCL pH 8.0, and 0.01%

Triton X-100) at 50°C for 20 min. Hybridized arrays were stained with 5.0 μg/ml streptavidin-phycoerythrin (Molecular Probes) and 2.0 mg/ml acetylated BSA (Sigma) in 1X ST-T at 40°C for 15 min. The streptavidin-phycoerythrin step was repeated after an intermediate amplification step in which anti-streptavidin rabbit IgG antibodies and secondary biotinylated goat anti-rabbit antibodies are added to the samples. Following washes, probe arrays were scanned twice at 6 μm resolution using the GeneChip system confocal scanner.

Microarray Data Collection and Analysis. Scanned image files were converted to mRNA expression levels using Affymetrix GeneChip3.1 software. This software assesses presence or absence of transcripts for each probe set, taking into account metrics such as background, noise, and comparison of intensities between Perfect Match (PM) and their control Mismatch (MM) probe cells. The average intensity of each microarray was scaled to a target intensity of 1500. Files containing the average difference intensity values (*i.e.*, expression levels) for each probe set were imported into an Access database. We assigned an arbitrary minimal expression level (*i.e.*, average difference) value of 20 to any negative or zero values prior to performing the statistical analysis.

Selection of Discriminatory Genes. Statistics. Several statistical measures have been introduced to identify differentially expressed genes for two conditions (*e.g.*, cancerous and normal tissues). Parametric tests such as P-value (Golub *et al.*, 1999) and t-test (Thomas *et al.*, 2001) are based on differences of group means, while non-parametric tests such as Wilcoxon rank sum (Mann-Whitney) test are based on differences of rank sums in groups (Thomas et al. 2001). A couple of measures such as Wilks' lambda were also proposed for the identification of discriminatory genes in multi-classes (Dudoit *et al.*, 2001; Hwang *et al.*, 2002). All these parametric and non-parametric statistical tests eventually use parametric distributions such as t-distribution or F-distribution. Thus, these tests may perform poorly, resulting in producing many "false positives" or even "false negatives," due to violation of their underlying distribution assumptions. In many cases of t-test applications, it can be seen that a histogram of t-statistic values of all genes does not match with a t-distribution theoretically defined for a given number of array samples. This discrepancy between a real distribution (histogram) and a theoretical distribution leads to "false positives" or "false negatives."

The inventors propose a novel method that employs a non-parametric empirical estimation of a distribution, kernel density estimator, for any statistical measure used to detect differential expressions of genes in two or multiple conditions (Wand and Jones, 1995). In this study, for each gene i, a log ratio (r_i) between expression levels of a MS sample (g_i^{MS}) and the mean of healthy samples (g_i^{H}) is calculated as a statistical measure, as shown in equation 1 (Lock et al. 2002).

$$r_i = \log_{10}\left(\frac{g_i^{MS}}{g_i^{H}}\right) \quad (1)$$

Then, an empirical distribution of those ratios, which can be used for the statistical hypothesis test to select differentially expressed genes, is obtained using kernel density estimator. The density for a certain ratio (r) is defined by n ratios (r_i) as shown in equation 2.

$$\hat{f}(r;h) = (nh)^{-1}\sum_{i=1}^{n} K\left(\frac{r - r_i}{h}\right) \quad (2)$$

Here, K is a function satisfying $\int K(x)dx = 1$, which is called the *kernel* (normal distribution in this study), and h is a positive number, usually called the *bandwidth* or *window width*. FIG. 1 shows a kernel density estimate constructed using five ratios (five "x" marks on the x-axis) with a kernel chosen to be the normal distribution with zero mean and unit variance ($N(0,1)$).

In Fig. 1, the solid line is the kernel density estimated from the five ratios or kernels (dotted line) each of which is centered to each ratio. Just as a bin size, called the *smoothing parameter*, should be correctly chosen to explore the structure or shape of the distribution, the bandwidth should be optimally determined. A small bandwidth results in an under-smoothed estimate, while a large bandwidth an over-smoothed estimate. This sensitivity of the distribution shape to the bandwidth size is called *variance-bias tradeoff*. The optimal bandwidth is selected to minimize the mean integrated squared error (MISE) between the estimated density ($\hat{f}$) and the target density (f) for the kernel $N(0,1)$, as shown in equation 3.

$$\hat{h} = \left[\frac{8\pi^{1/2} R(K)}{3\mu_2(K)^2 n}\right]^{1/5} s \qquad (3)$$

Here, $R(K)$ and $\mu_2(K)$ are defined by $\int K(r)^2 dr$ and $\int r^2 K(r) dr$, respectively, and s is the estimated standard deviation of ratios. Since this bandwidth to minimize MISE tends to be large, we tried $\hat{h}/2$, $\hat{h}/4$, and $\hat{h}/8$ to choose an optimal bandwidth among those derived from the MISE criterion in terms of the variance-bias tradeoff. In most of cases, $\hat{h}/2$ produced the optimal distribution structure (Wand and Jones, 1995). FIG. 2A shows a kernel density estimate for a MS sample where the optimal bandwidth is 0.052 and FIG. 2B shows a histogram with a bin size equivalent to the determined bandwidth. The kernel estimate indicates that there are two clear modes and one weak mode in the distribution. One clear mode in the left and one weak mode in the right of the distribution imply that there are more down-regulated genes in MS than up-regulated genes. Also, the mode in the center means that the majority of genes are not differentially expressed in MS and healthy patients. Comparing the kernel density estimate with the histogram, we can see that this estimated distribution matches well with the histogram.

With this empirically estimated distribution, a typical two-tailed hypothesis test is performed, as the typical t-test is done with t-distribution. The null hypothesis (H_0) is that means are equal and the alternative hypothesis (H_1) is that means are not equal. For instance, for a ratio marked on the x-axis in FIG. 2A, the area under the distribution below the ratio (a_i in equation 4) is calculated, and then the probability (called significance) of observing the given result by chance, when the null hypothesis is true, is determined as shown in equation 4.

$$p_i = 2\min(a_i, 1 - a_i) \qquad (4)$$

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All of the compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

VII. REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

U.S. Patent 3,817,837

U.S. Patent 3,850,752

U.S. Patent 3,939,350

U.S. Patent 3,996,345

U.S. Patent 4,275,149

U.S. Patent 4,277,437

U.S. Patent 4,366,241

U.S. Patent 4,683,195

U.S. Patent 4,683,202

U.S. Patent 4,684,611

U.S. Patent 4,797,368

U.S. Patent 4,800,159

U.S. Patent 4,883,750

U.S. Patent 4,952,500

U.S. Patent 5,139,941

U.S. Patent 5,242,974

U.S. Patent 5,279,721

U.S. Patent 5,302,523

U.S. Patent 5,322,783

U.S. Patent 5,384,253

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U.S. Patent 5,851,772
U.S. Patent 5,853,990
U.S. Patent 5,853,992
U.S. Patent 5,853,993
U.S. Patent 5,856,092
U.S. Patent 5,858,652
U.S. Patent 5,861,244
U.S. Patent 5,863,732
U.S. Patent 5,863,753
U.S. Patent 5,866,331
U.S. Patent 5,866,336
U.S. Patent 5,882,864
U.S. Patent 5,900,481
U.S. Patent 5,905,024
U.S. Patent 5,910,407
U.S. Patent 5,912,124
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U.S. Patent 5,919,630
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U.S. Patent 5,932,451
U.S. Patent 5,935,791
U.S. Patent 5,935,819
U.S. Patent 5,935,825
U.S. Patent 5,939,291
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